Statistical Challenges in Biomedical Research

NASA Johnson Space Center

SLSSI Lecture Series

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Biostatistics Laboratory

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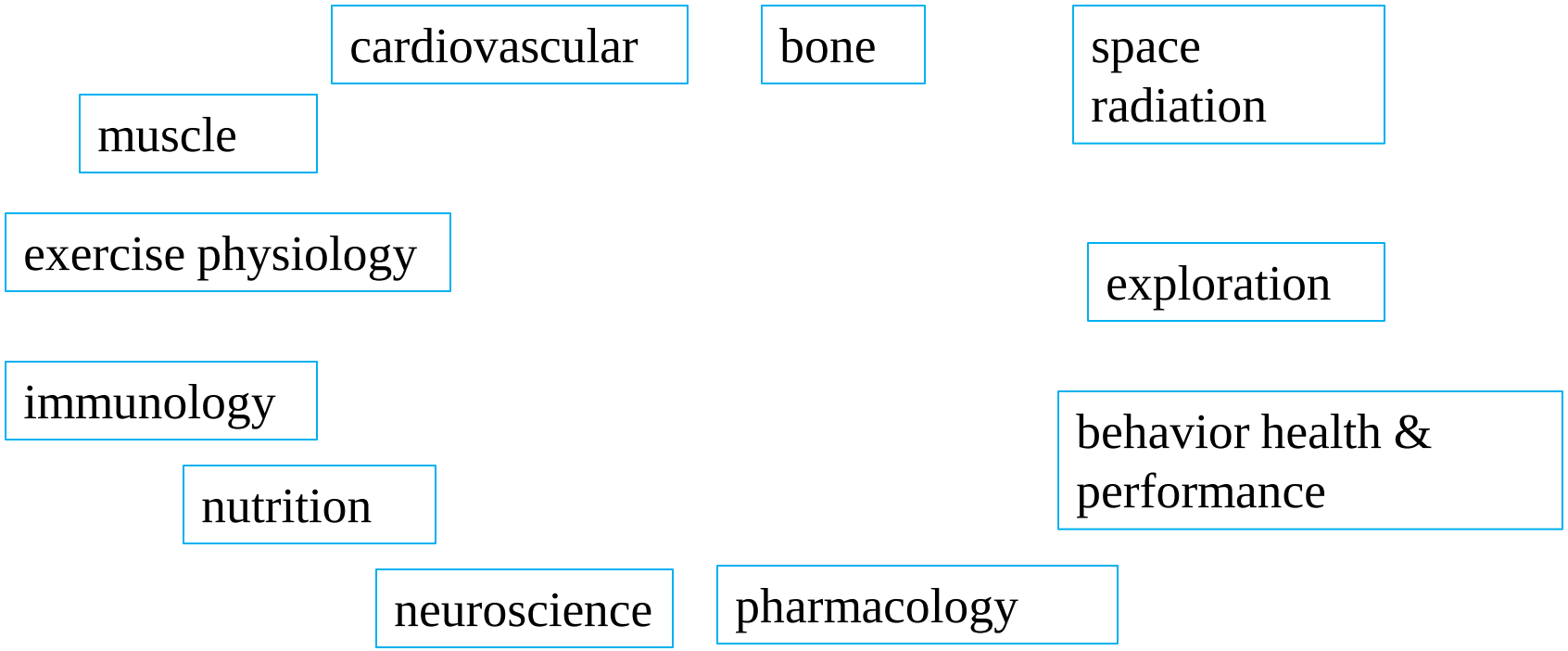
HACD Laboratories and Human Research Program Elements



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- develop countermeasures

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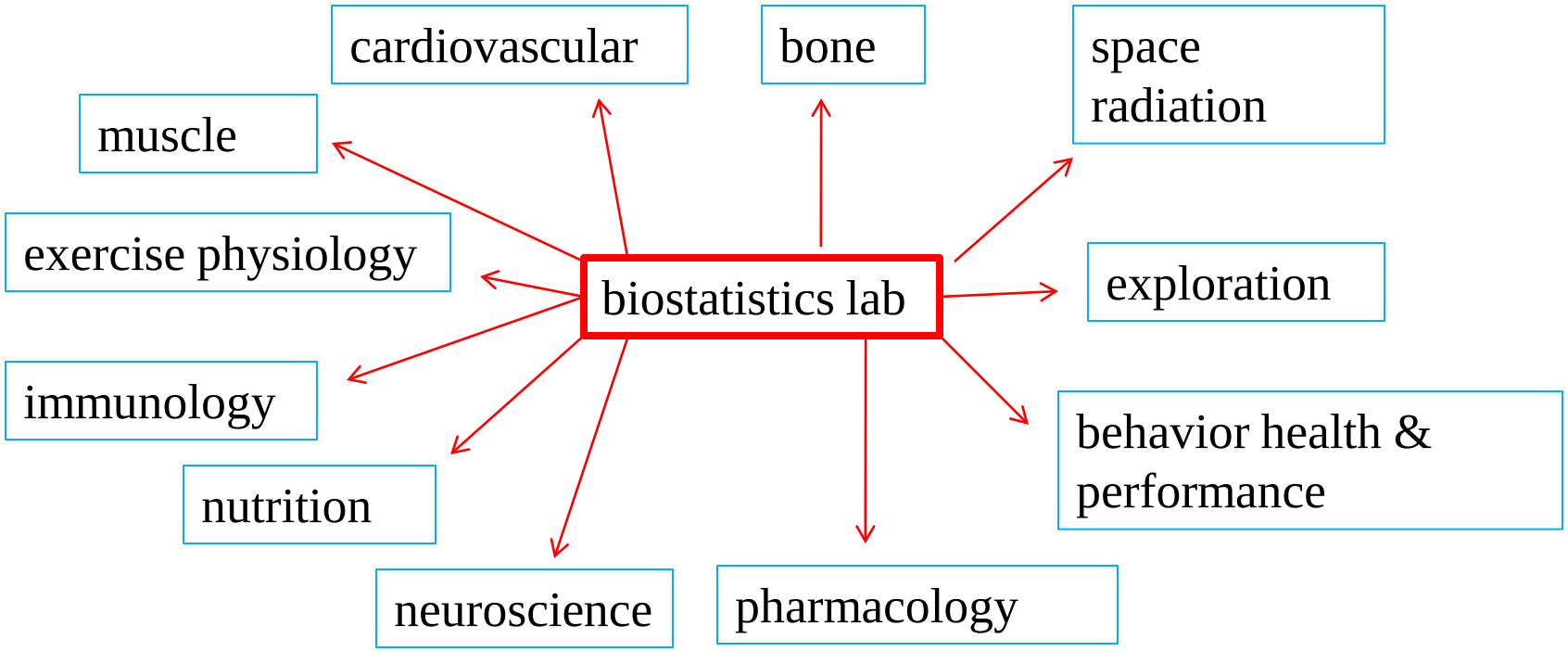

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Potentially Debilitating Effects of Spaceflight Environment

- **Bone Demineralization – Osteoporosis**
- **Impaired Fracture Healing – Non-Union**
- **Renal Stone Formation & Soft Tissue Calcification**
- **Orthostatic Intolerance (on return to gravity)**
- **Cardiac Arrhythmias**
- **Dehydration (on return to gravity)**
- **Decreased Aerobic Capacity**
- **Impaired Coordination**
- **Muscle Atrophy (Loss of Strength)**
- **Radiation Sickness**
- **Increased Cancer Risk**
- **Impaired Immune Function**
- **Behavioral Changes & Performance Decrements**
- **Altitude Decompression Sickness during EVA**

Research Venues

Flight Experiments

- long-duration space missions
- short-duration space missions
- parabolic trajectory aircraft

Ground-based analog experiments

- bed-rest (unloading of bones,muscles)
- Antarctica (isolation)
- NEEMO (isolation + confinement)
- Houghton-Mars (exploration, space medicine)

Ways in which the Biostatistics Laboratory participates in the research process:

Design of experiments

- numbers of subjects
- how often measurements are made

Extracting information from experiment data

- develop or suggest data analysis procedures
- perform data analysis

Reporting results

- presentations
- assist with manuscript preparation for publication

Constraints

- extremely limited human subject pool
- support of NASA operations must be maintained

Dependent Measures
(examples)

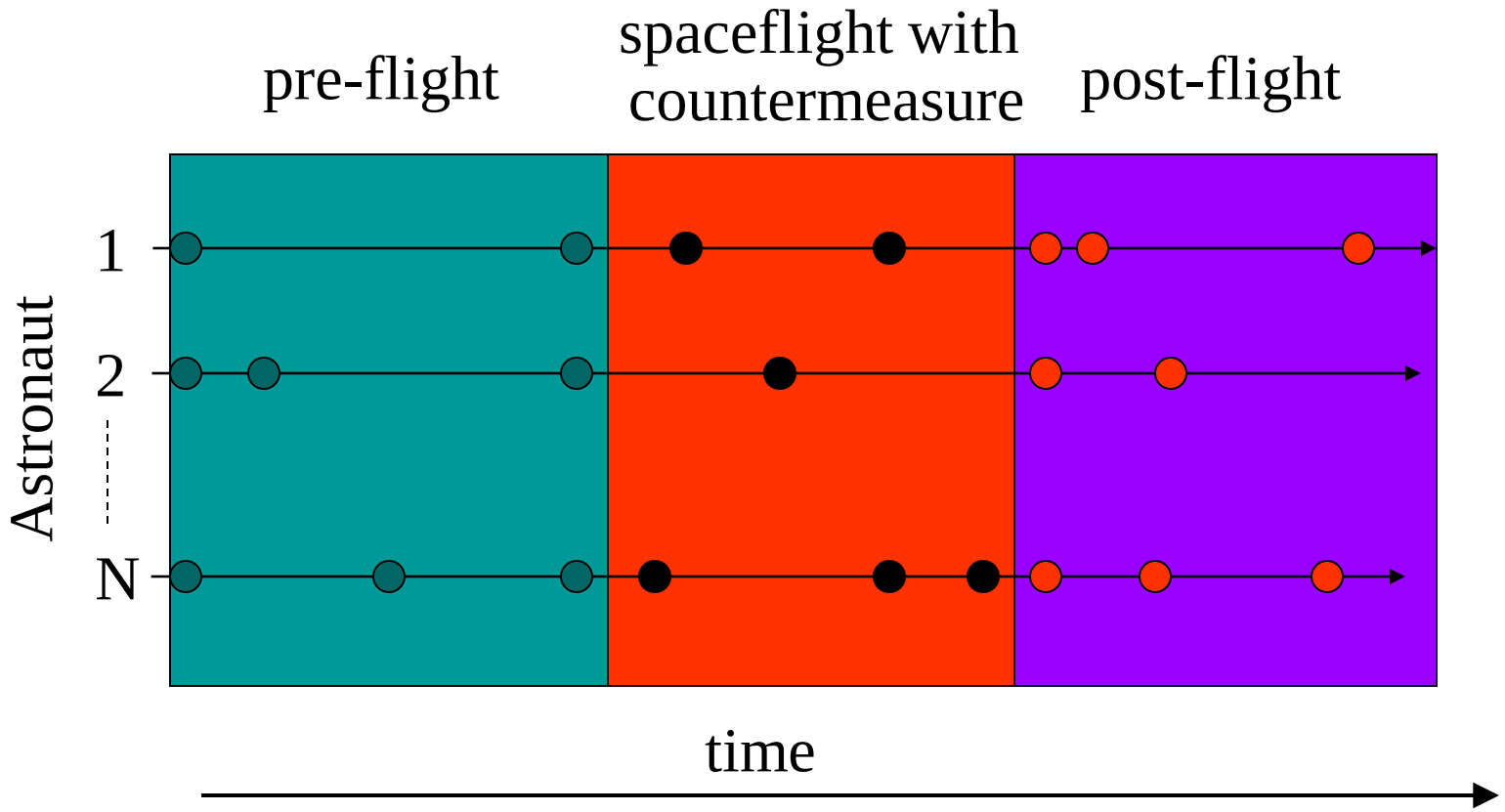
- Clinical

  ECG, bone density, muscle strength, urinalysis, blood, standard neuro, eye exams, VO_2 max, HR

- Specialized

  locomotion performance, nutritional markers, tilt test time, balance control, viral reactivation, cytokine production, buckling ratio, subjective sleepiness or discomfort scores

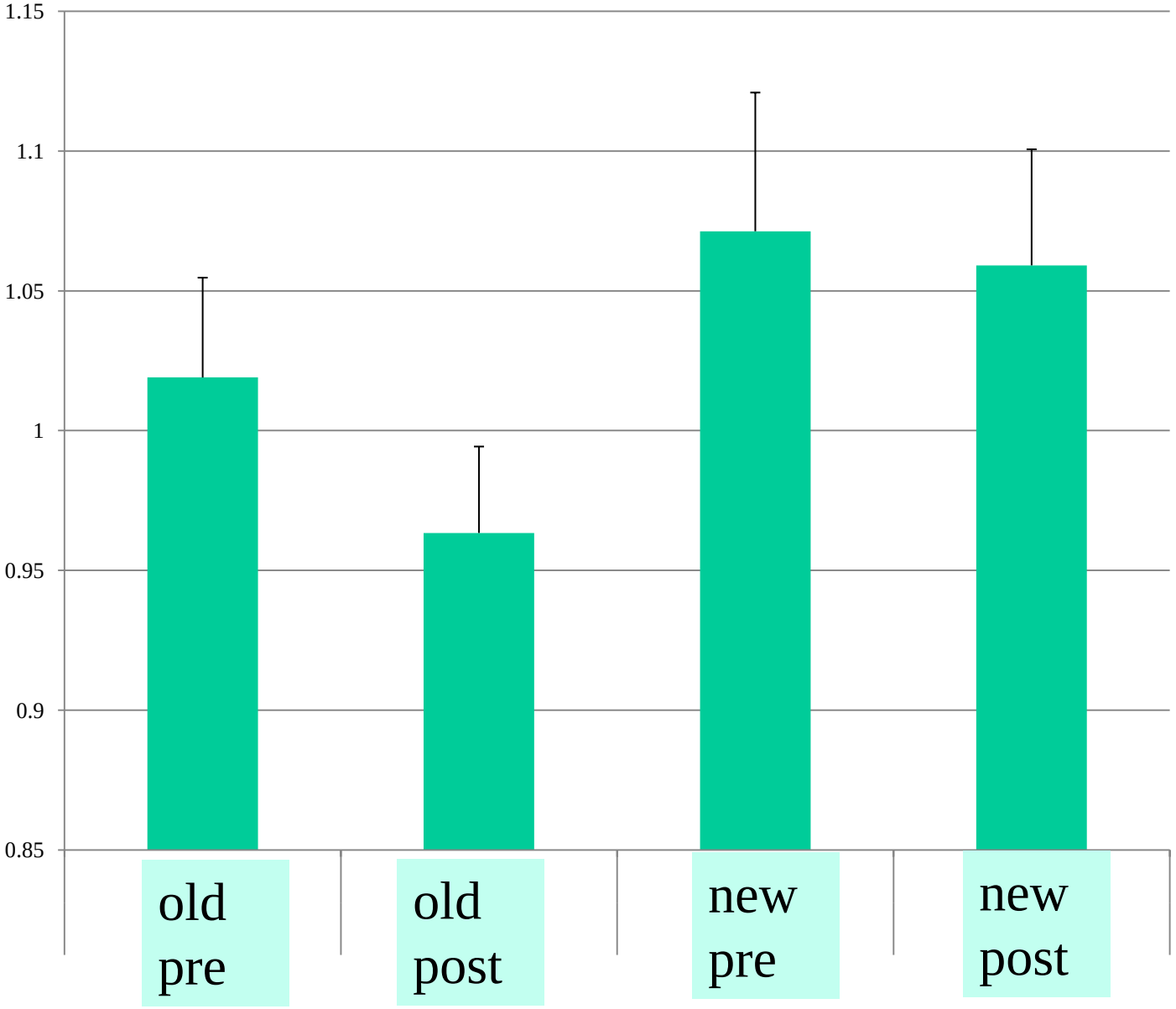
Longitudinal Setting

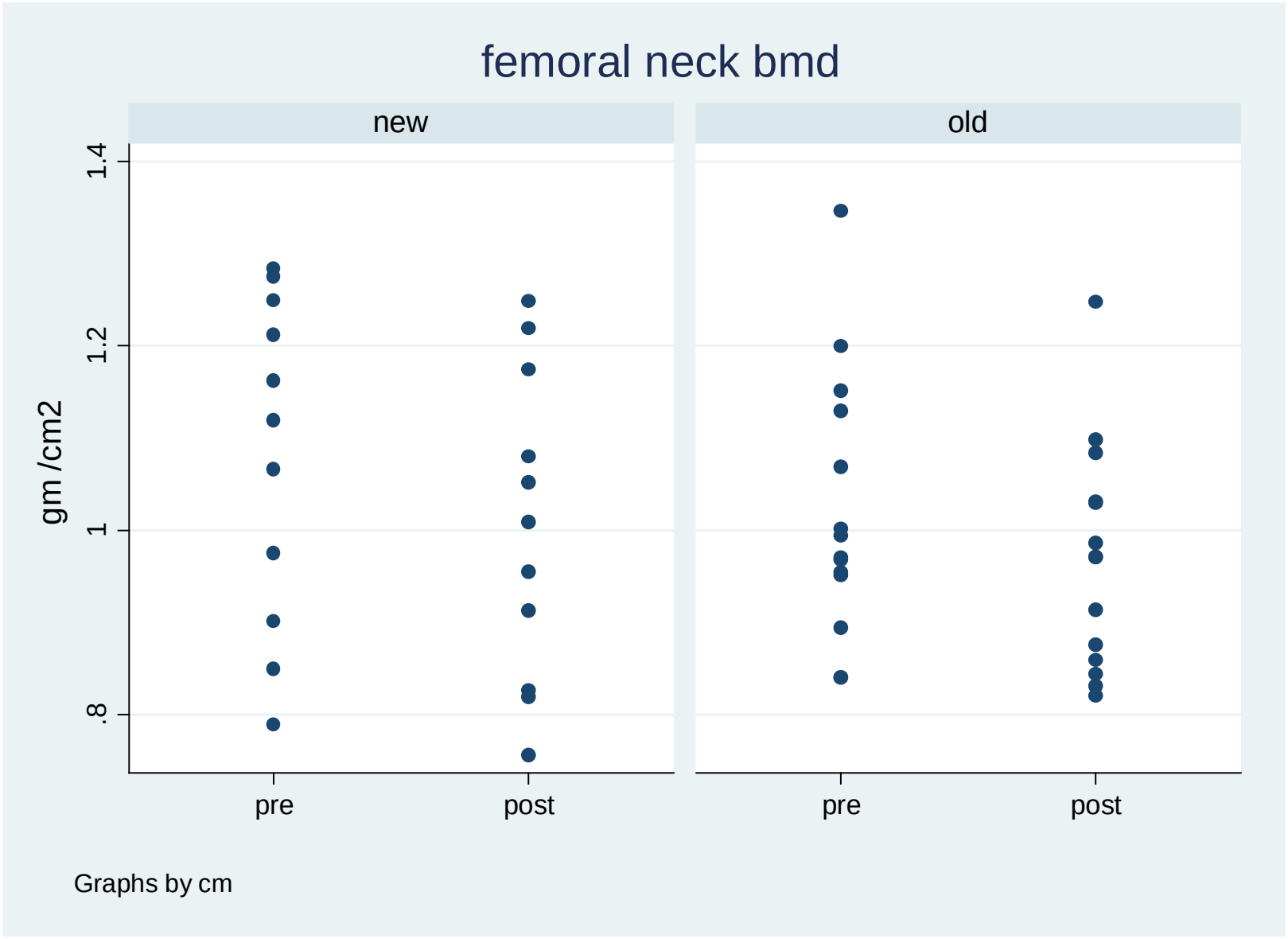


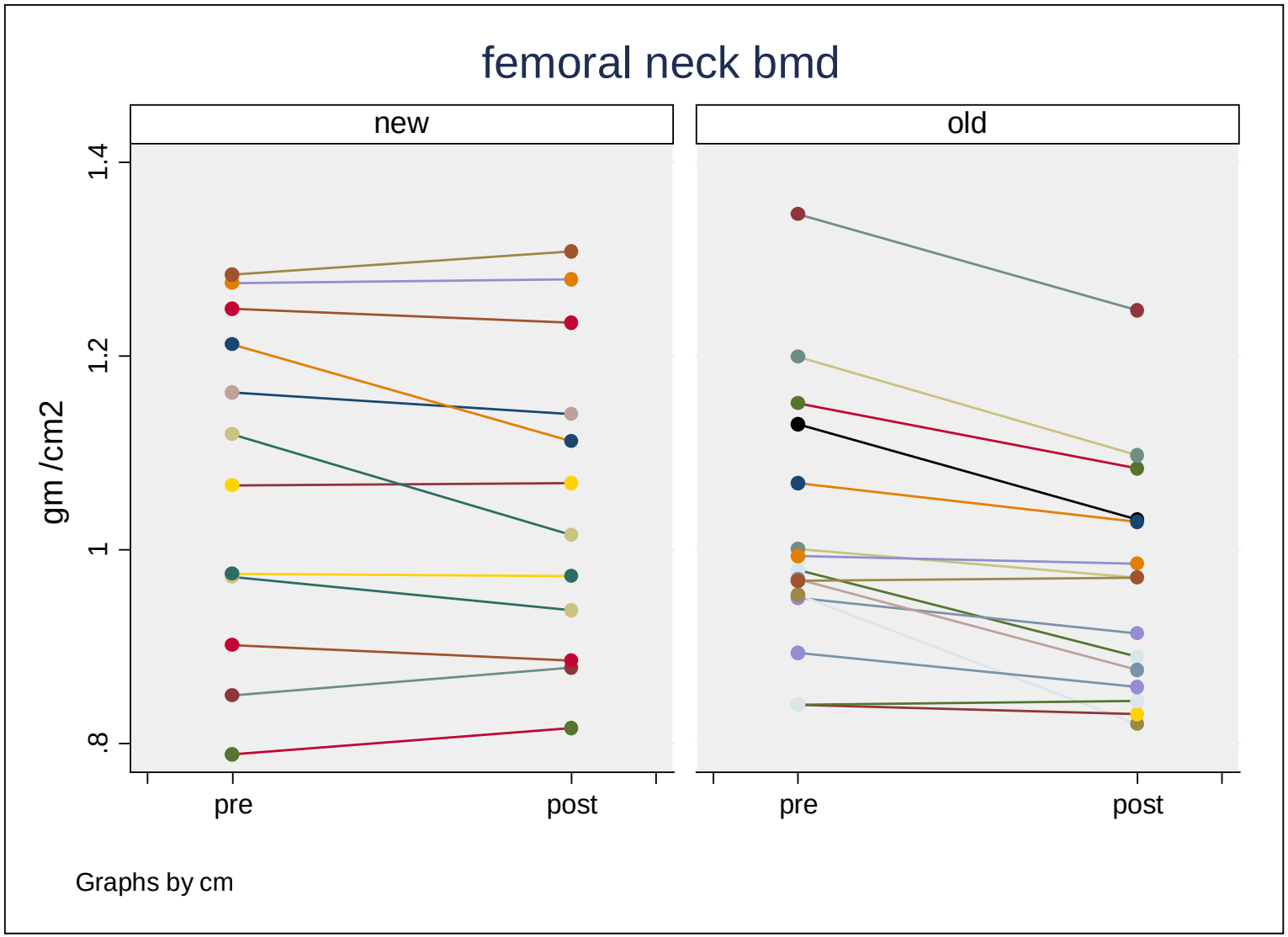
Statistical challenges

- effective display of data
- longitudinal data (pre, in , post-flight)
- high variability between subjects
- highly unbalanced design (dictated by operations)
- multivariate measurements
- rich variety of distributions
    - skewed
    - limited range
    - time-to-event (“survival”)
    - discrete
    - zero-inflated
- multiple imputation
- models for simulation
- sample size / power estimation
- model selection - multiple testing

femoral neck bmd




femoral neck bmd
new
old
gm /cm2
1.4
1.2
1
.8
pre
post
pre
post
Graphs by cm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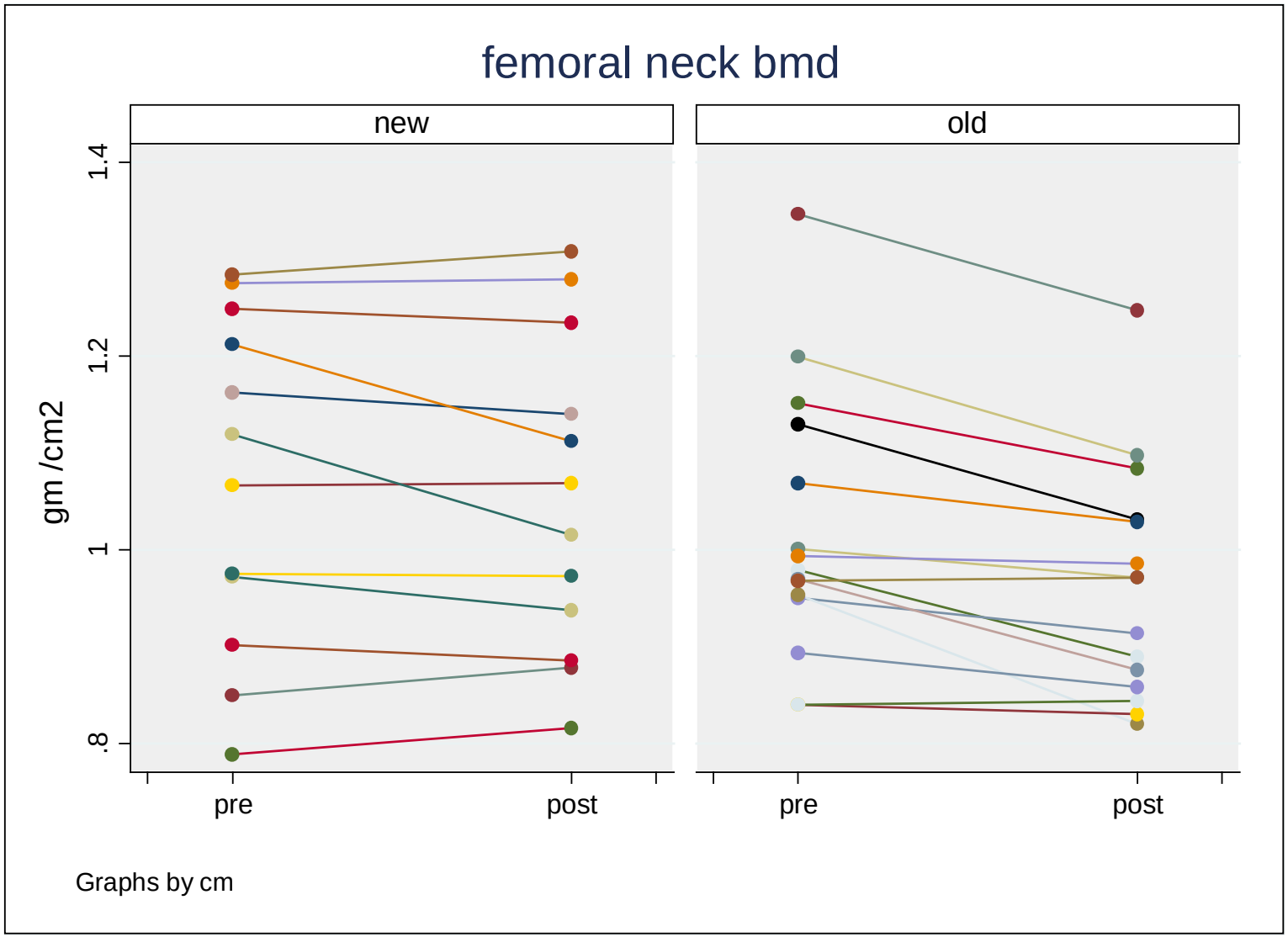


Is the new CM any better than the old?

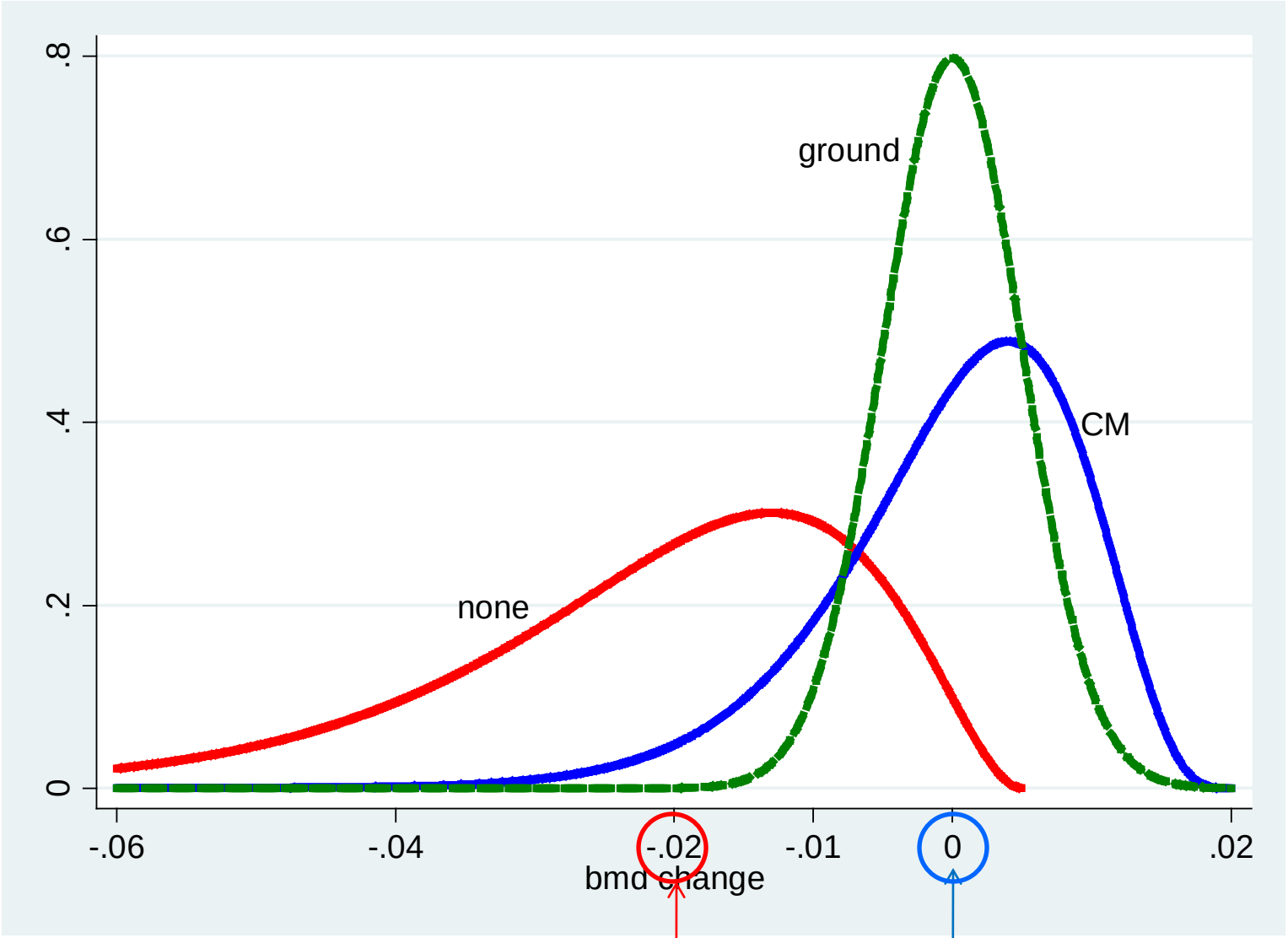
Typical approach:

Judge effectiveness by difference in means.

Alternative approach:

Judge effectiveness by difference in percent of population protected against a big loss.

effect of CM on mean change in bmd



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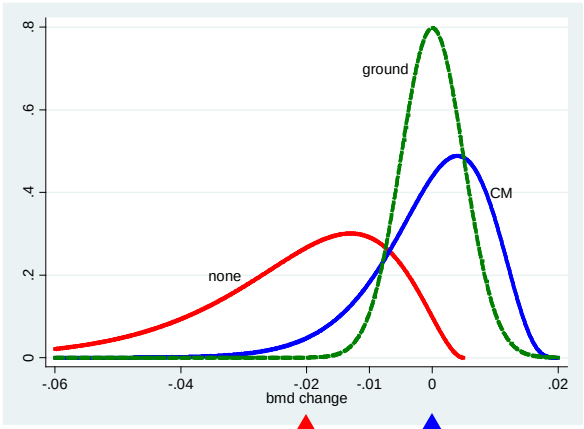
How?

- Estimation with uncertainty interval

Ex. 0.020 ±0.008



-.02

0

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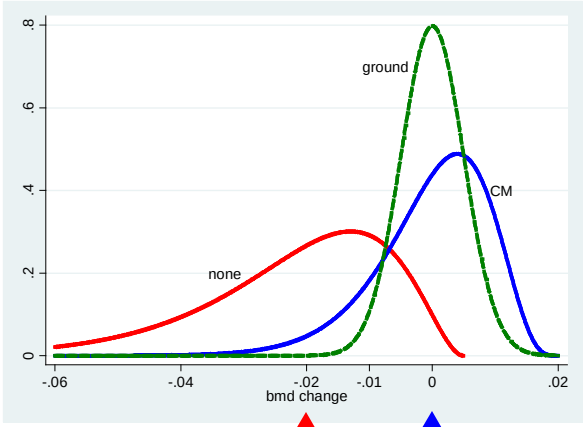
How?

- Estimation with uncertainty interval

  Ex. 0.020 ±0.008

- Statistical inference

  "P-value"



-.02 0

effect of CM on proportion of population protected

effect of CM on proportion of population protected

Typical approach:

Alternative approach:

How?

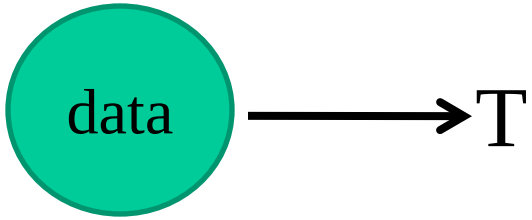
- Estimation with uncertainty interval

  Ex. 63% (33%, 78%)

- Statistical inference

Statistical Inference

Calculate something from the data (a “statistic” – call it “T”) that gets larger as the observed effect of the new CM relative to the old CM increases.



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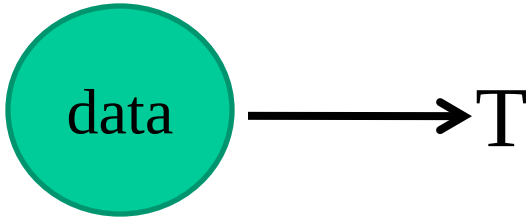

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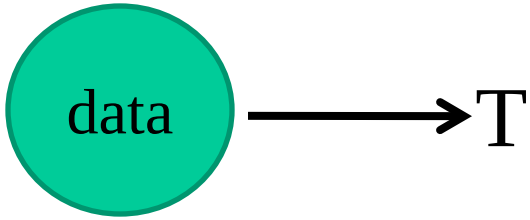

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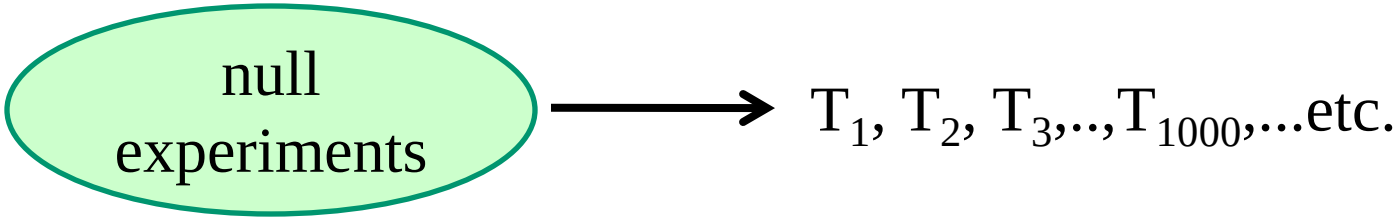
For each of these hypothetical experiments, imagine that T is recalculated.



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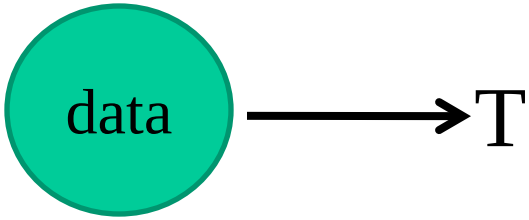

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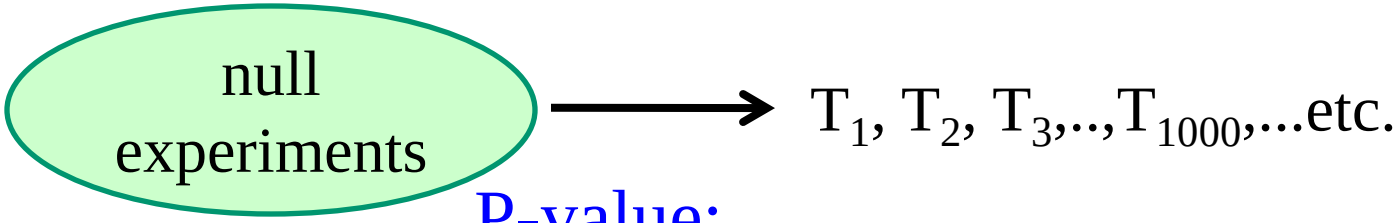


P-value:

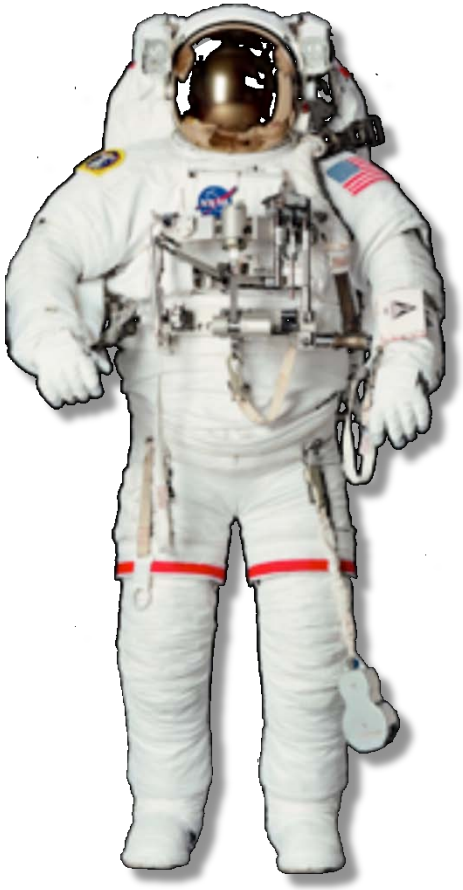
How likely is it that a "T" for one of these hypothetical null experiments would be greater than the value of T we calculated from the real data?

Examples of Projects, Data

- environmental physiology
- behavioral health and performance
- neurological
- bone
- radiation
- cardiovascular

Monitoring Metabolic Rate during EVA

- Spacesuit is a closed life-support system.
- Consumables are used up in proportion to how hard an astronaut is working (met rate).
- To predict how much longer an astronaut can safely continue an EVA, need to monitor his/her met rate (BTU/h).



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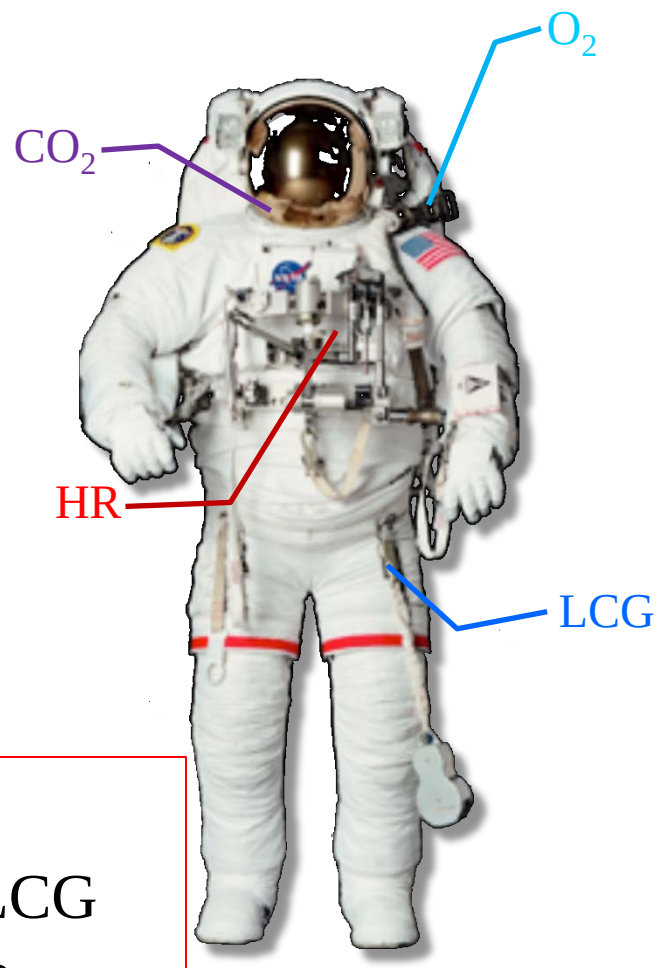

•Data:

•4 disparate sensors – O_2, CO_2, HR, LCG

•each provides an estimate of met rate

•all estimates have errors

Monitoring Metabolic Rate during EVA

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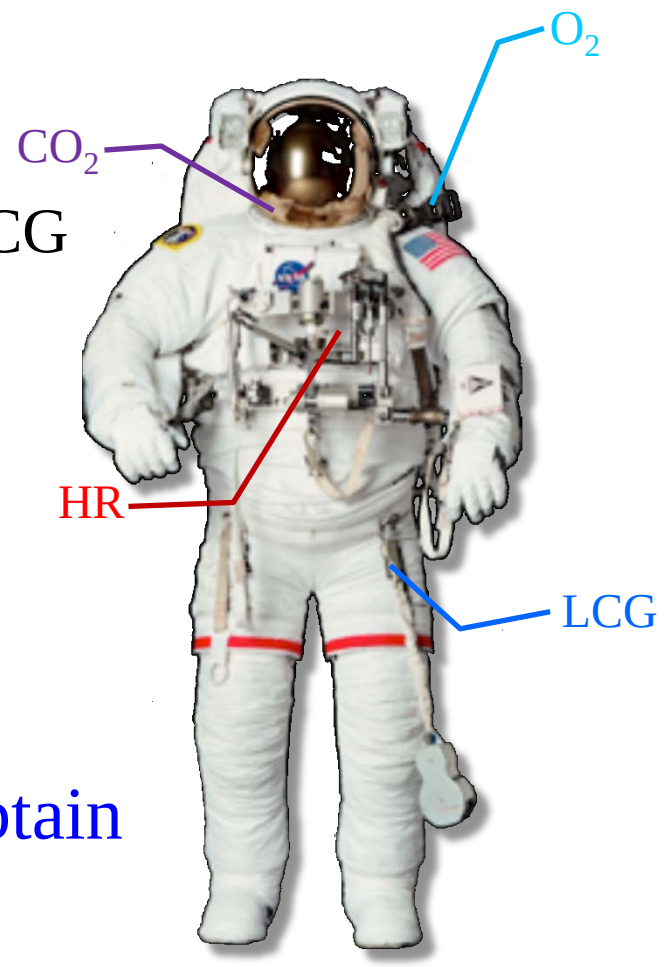
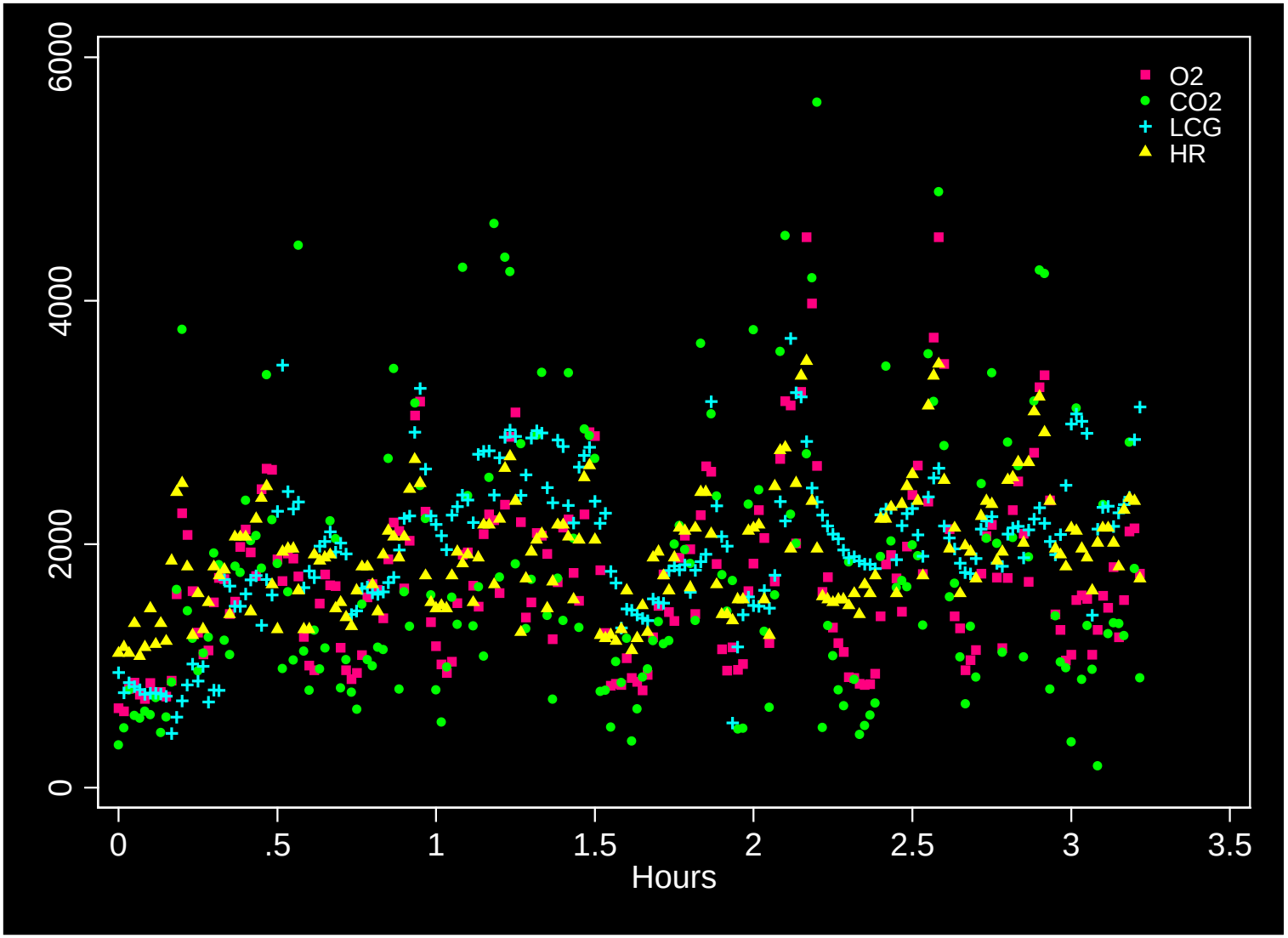


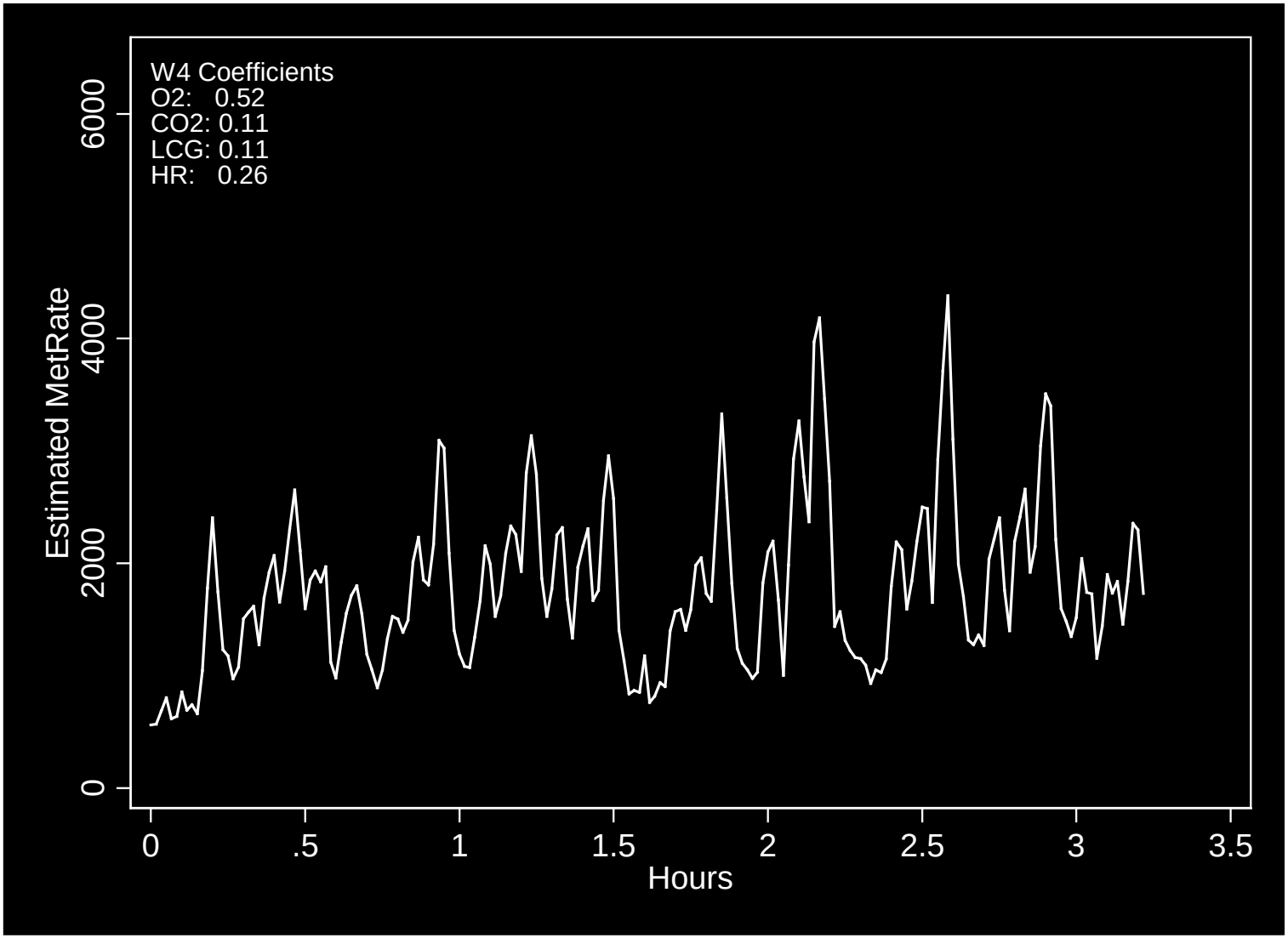
Problem:

How should one combine the individual met-rate estimates to obtain the most reliable single estimate?

What the data looks like?



Our “Best Estimate”



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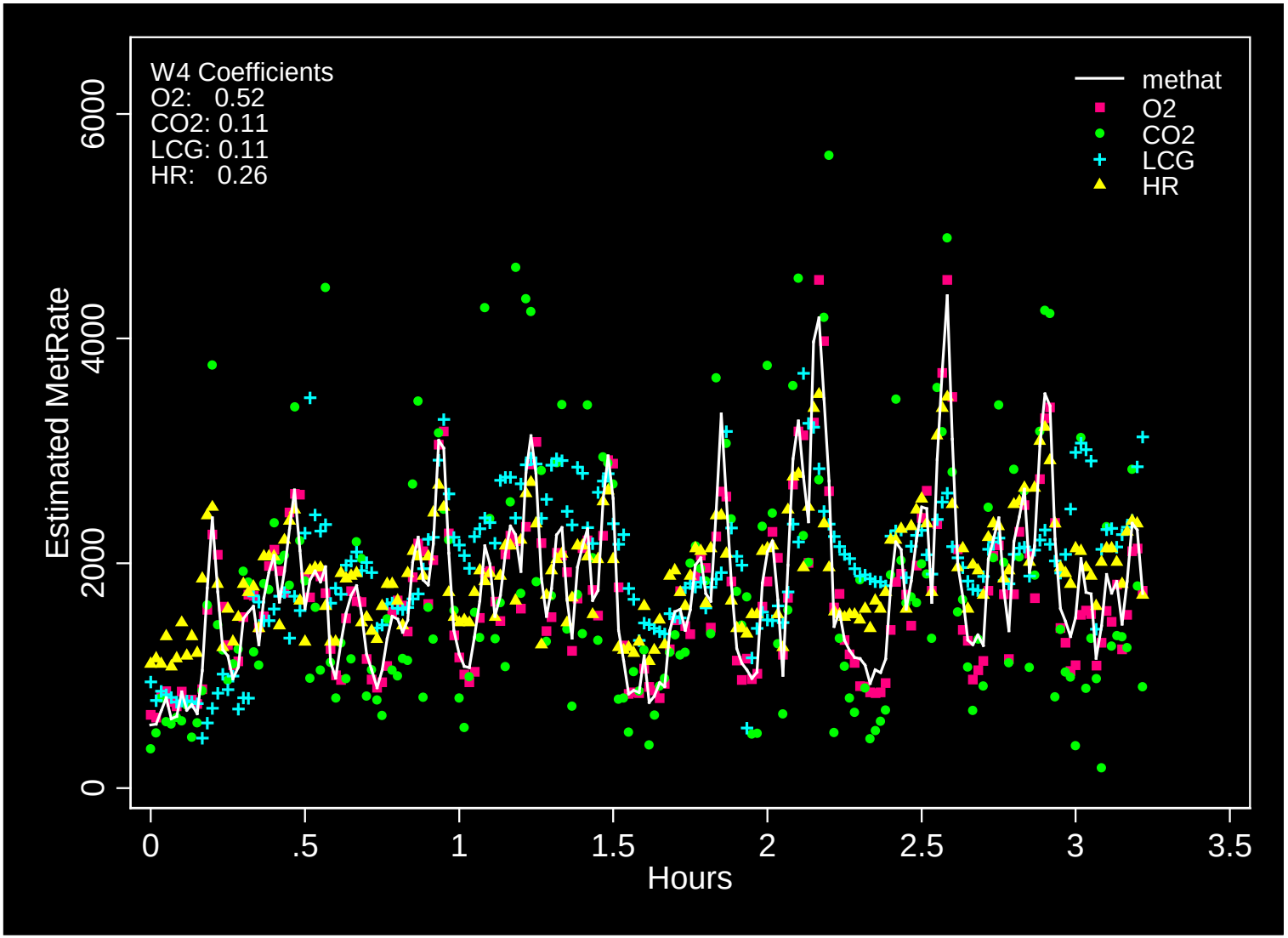

Techniques used

- thermal/gas-exchange models

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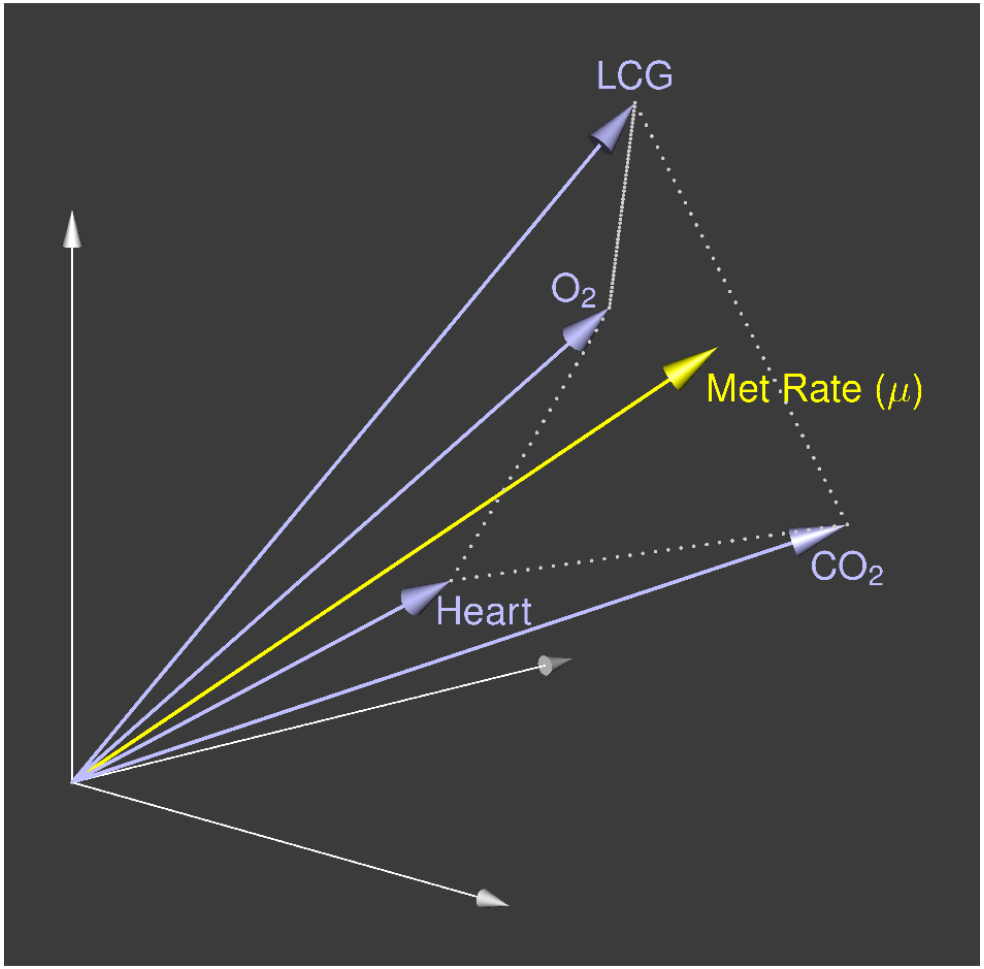
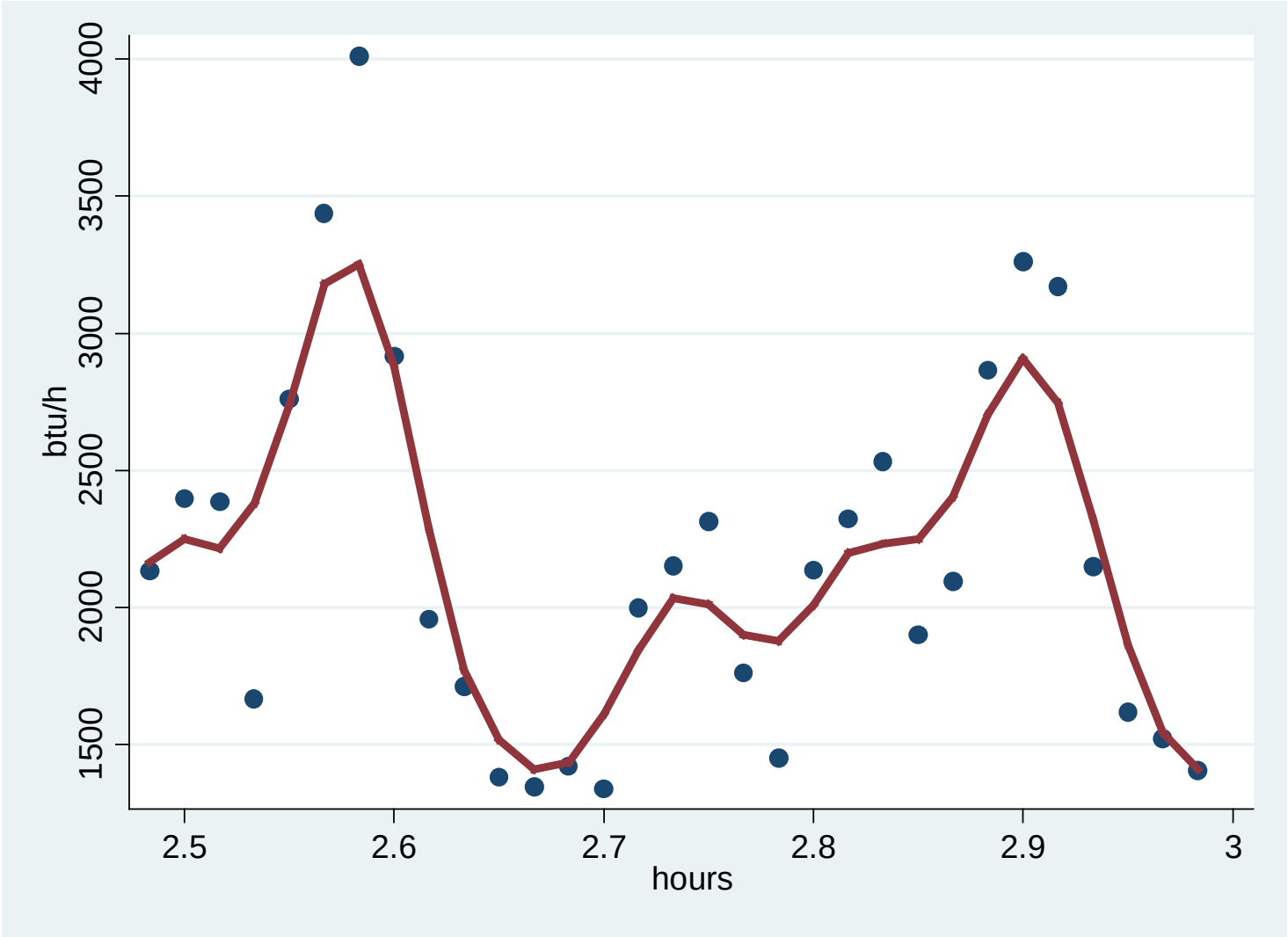


factor analysis model

Techniques used

- thermal/gas-exchange models
- factor analysis
- accuracy assessment using autoregressive error model



autoregressive error model

Examples of Projects, Data

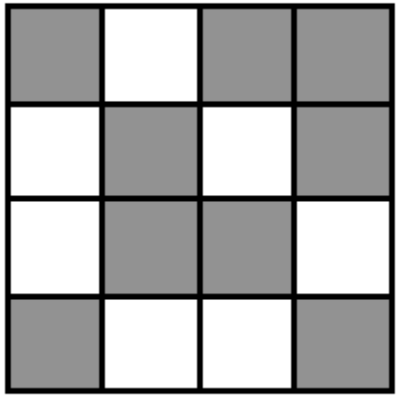
- environmental physiology
- behavioral health and performance
- neurological
- bone
- radiation
- exercise

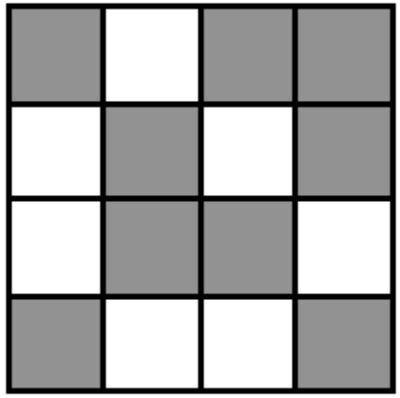
Compare two cognitive tests that are designed to show degraded performance with increasing sleepiness

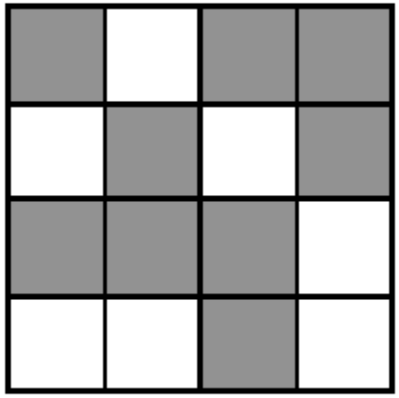
Subjects take promethazine (PMZ).

At each of 12 timepoints:

- measure PMZ concentration in blood
- obtain subjective report of sleepiness (1-9 scale)
- record cognitive test performance - Test1, Test 2







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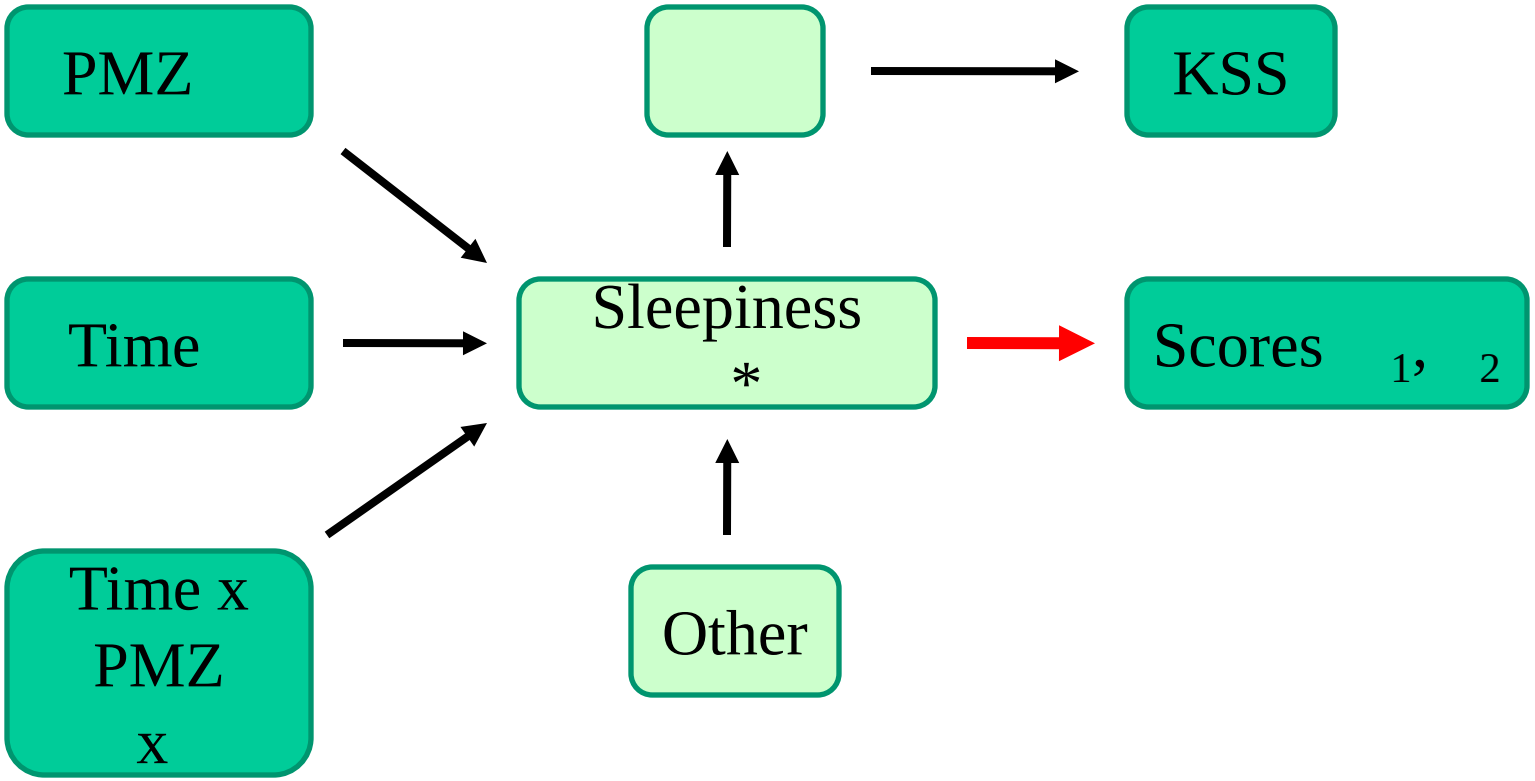
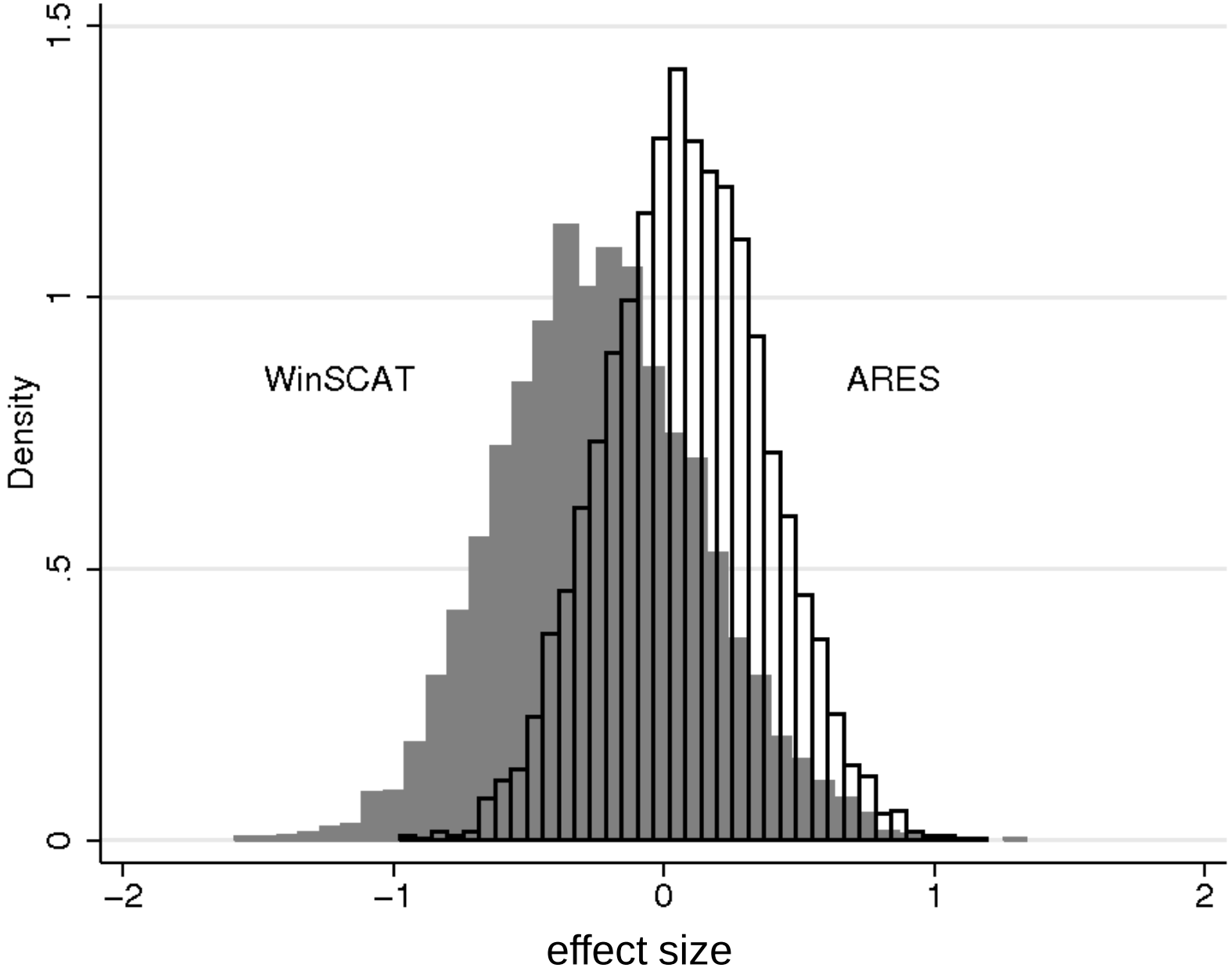
Which test is more sensitive to (true) sleepiness?

Latent Variable Model




1.5
1
.5
0
Density
WinSCAT
ARES
−2
−1
0
1
2
effect size

Examples of Projects, Data

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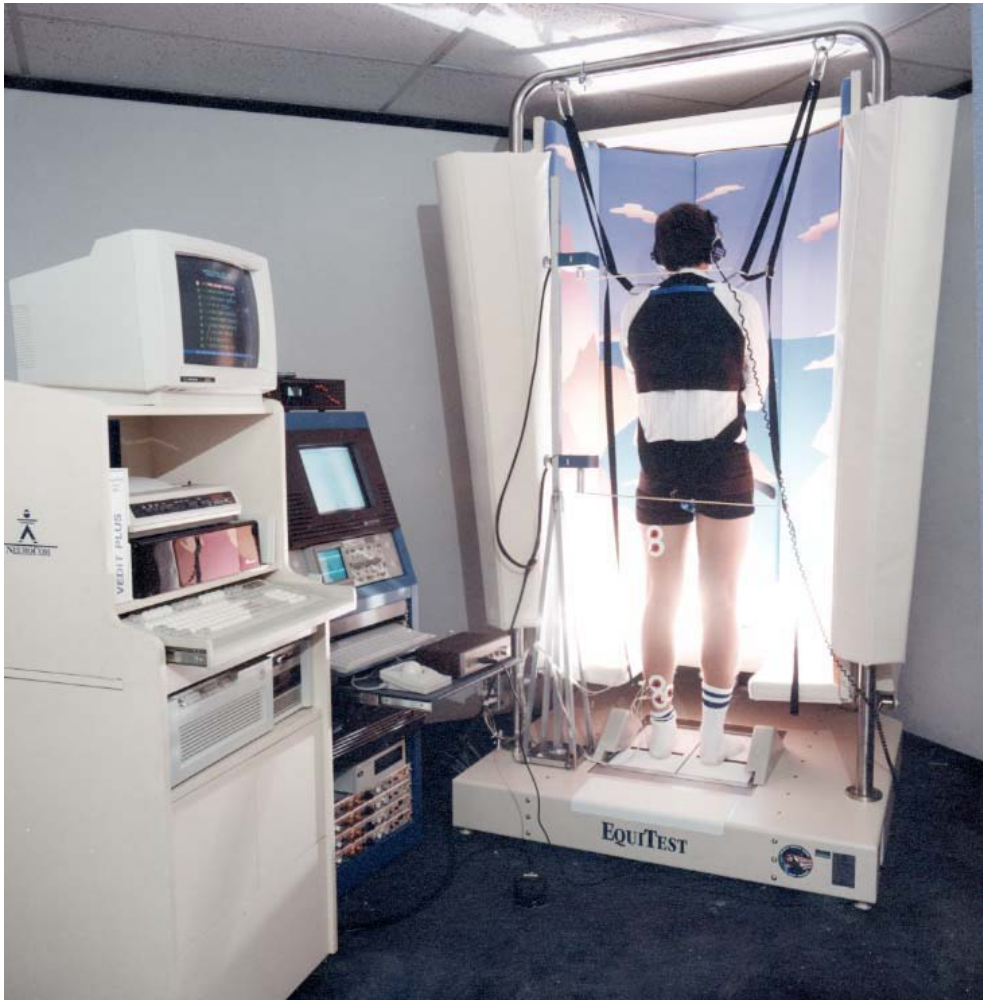
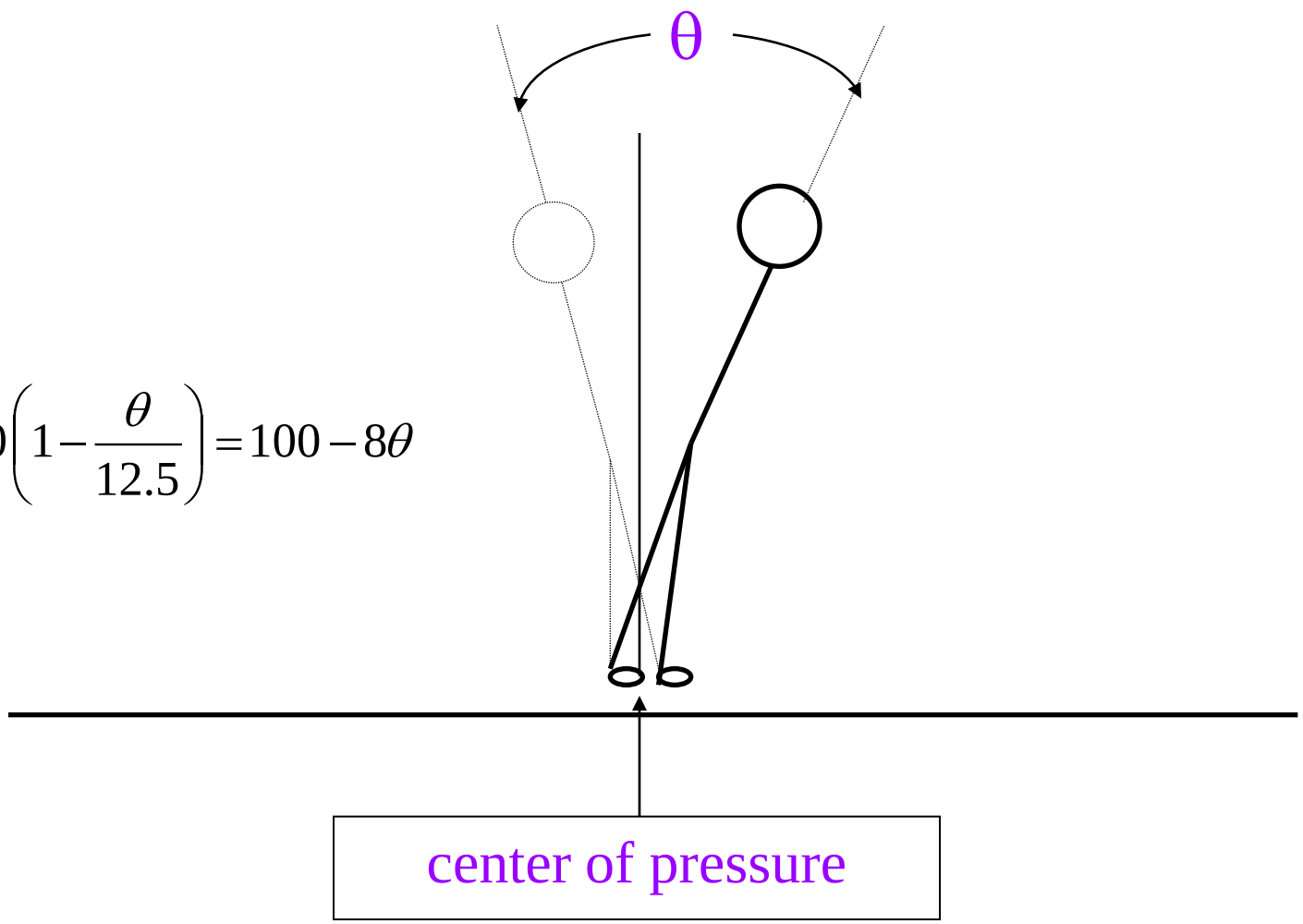
- neurological
- bone
- radiation
- exercise

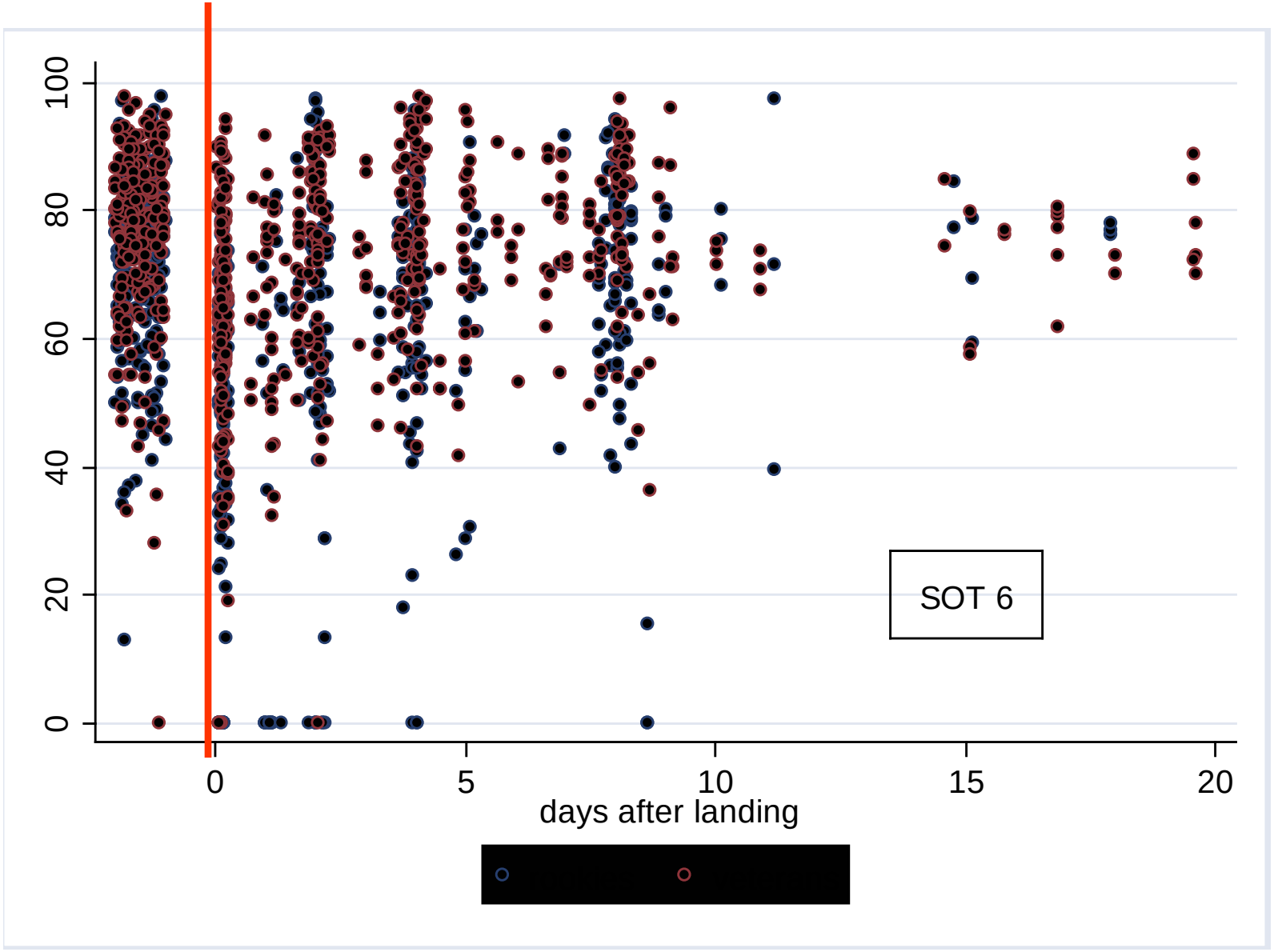
Sensory Organization Test (neurological)



$$= 100\left(1 - \frac{\theta}{12.5}\right) = 100 - 8\theta$$



Equilibrium Score



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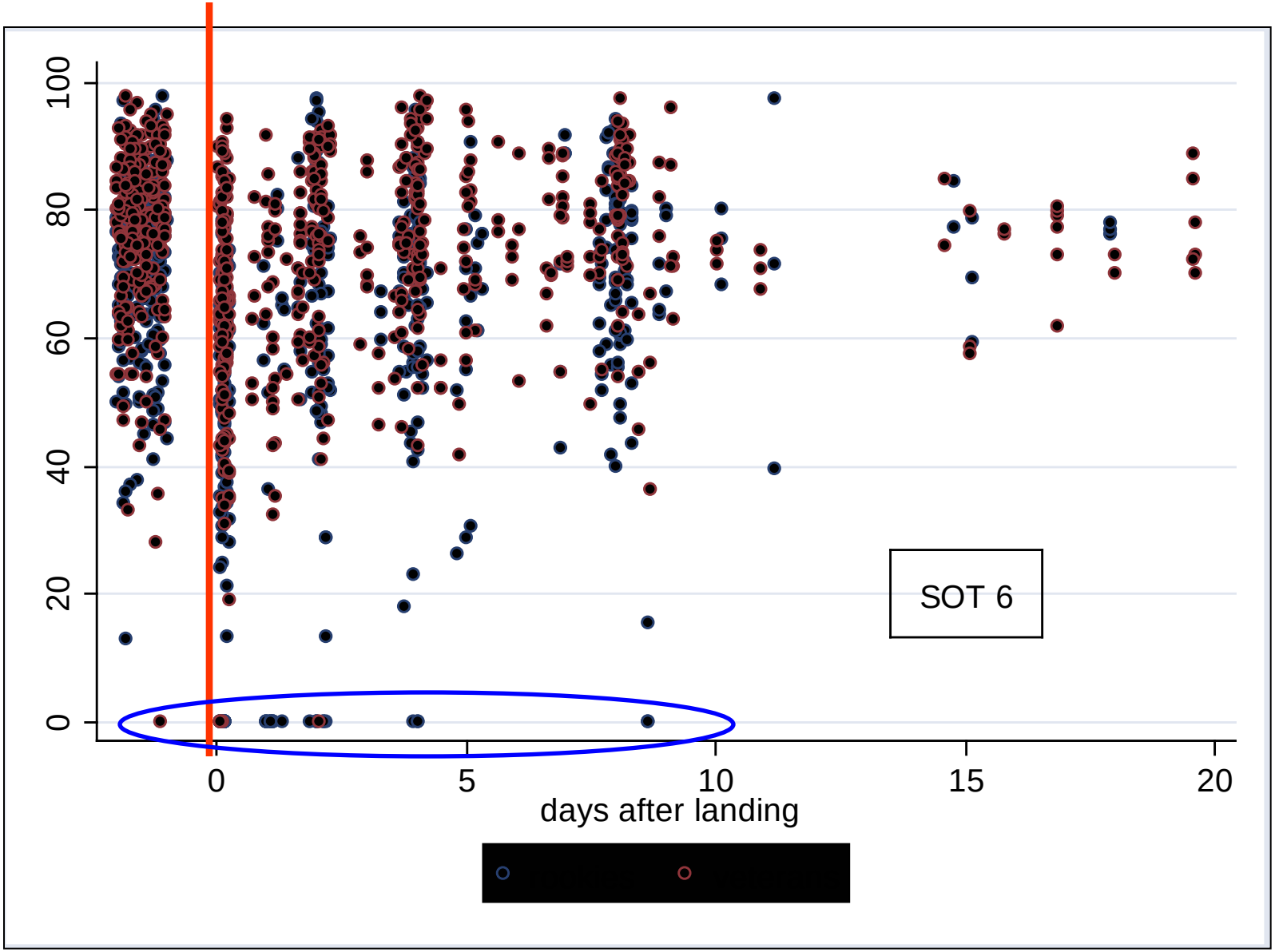
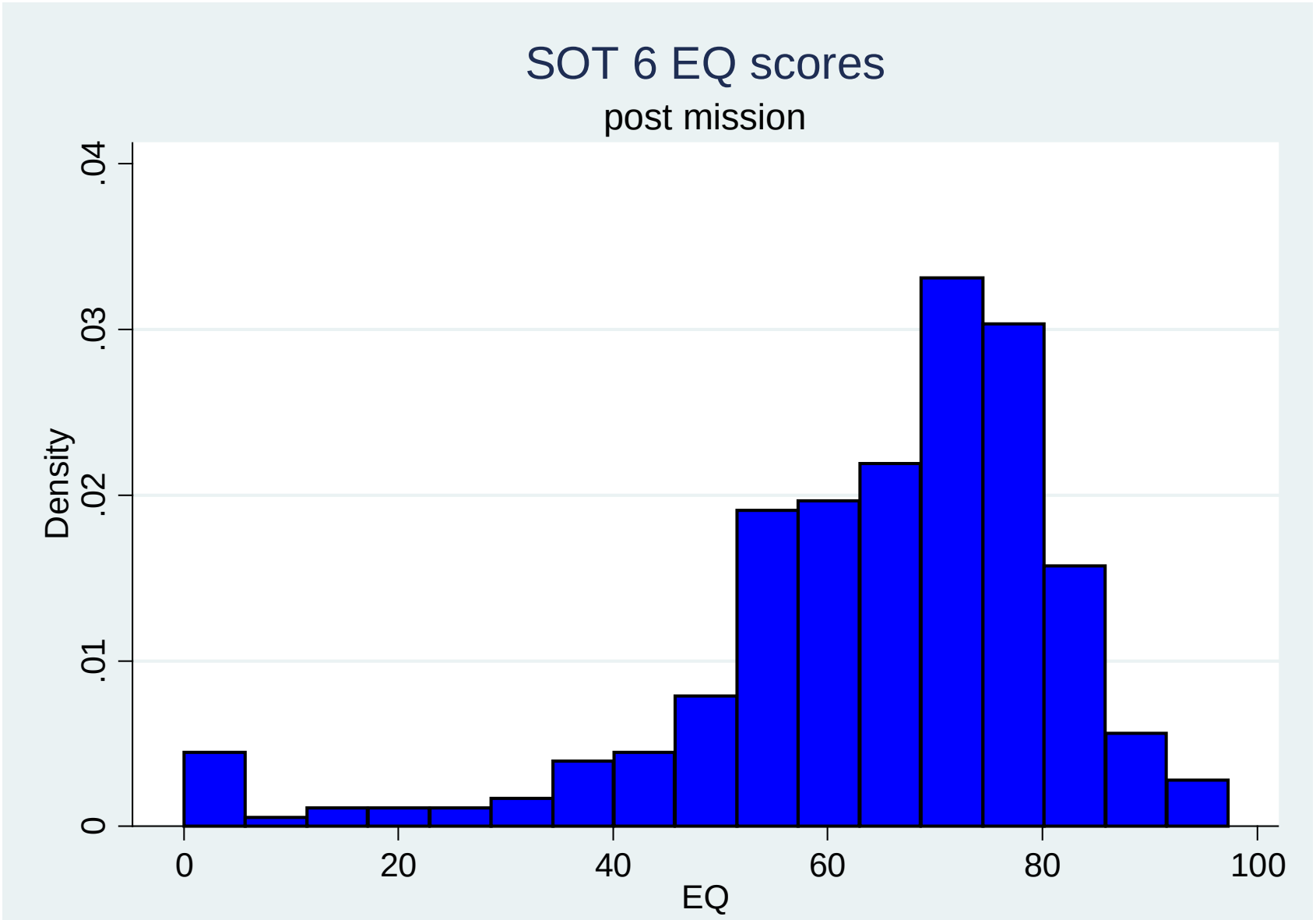


SOT Data

- longitudinal design
- limited range (0 – 100)
- left-skewed distribution


SOT 6 EQ scores
post mission
Density
0
.01
.02
.03
.04
0
20
40
60
80
100
EQ

SOT Data

- longitudinal design
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- left-skewed distribution
- falls

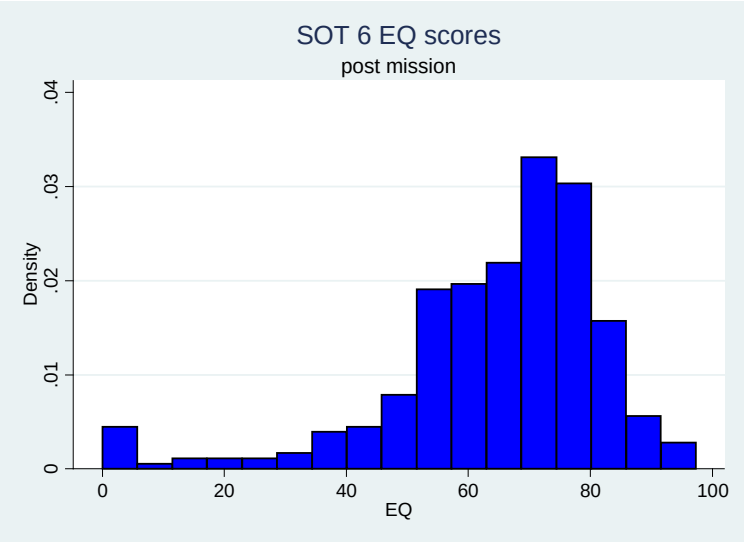
SOT Data

longitudinal design

limited range (0 – 100)

left-skewed distribution

falls



Score of zero for falls is arbitrary.

Averaging in a zero for falls is not valid:

e.g. (60, fall) is not the same as (30, 30).

SOT Data

longitudinal design

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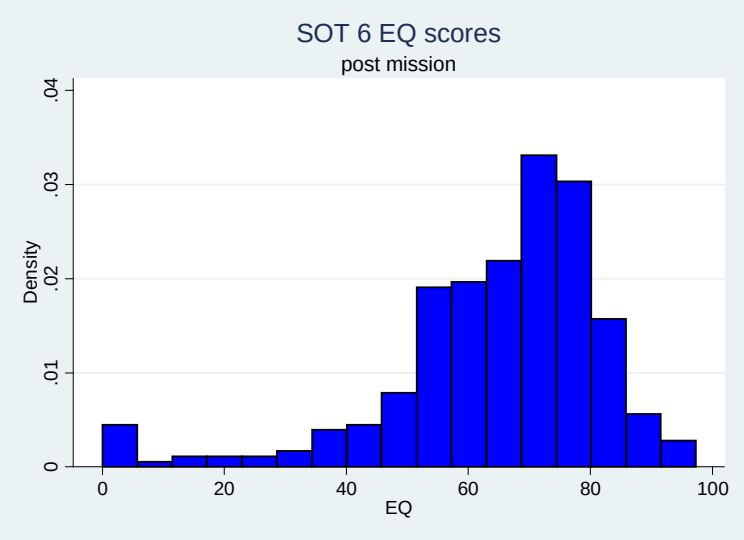
falls



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Use latent variable model to represent unobserved balance control ability when there is a fall.

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- neurological
- bone
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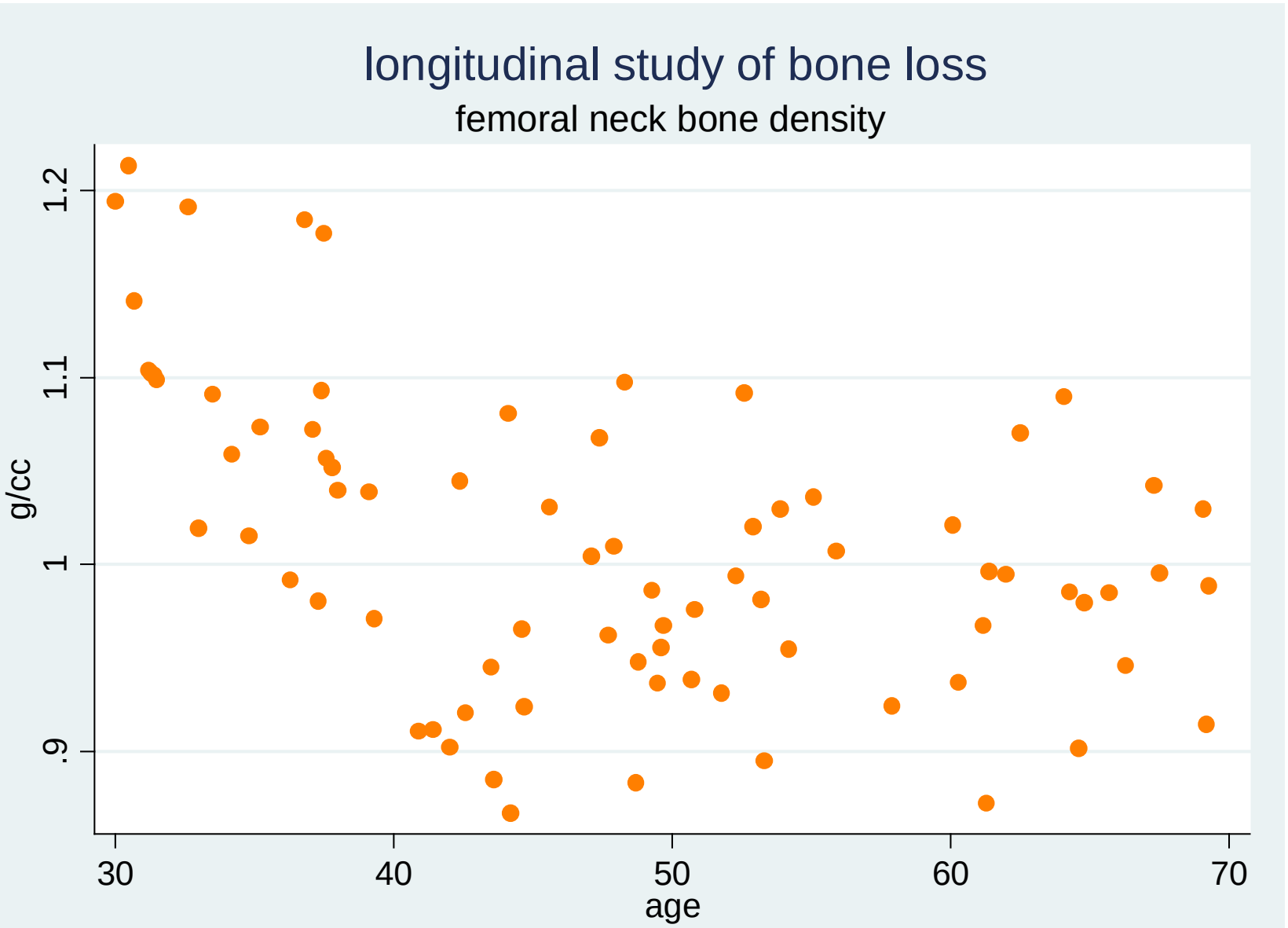
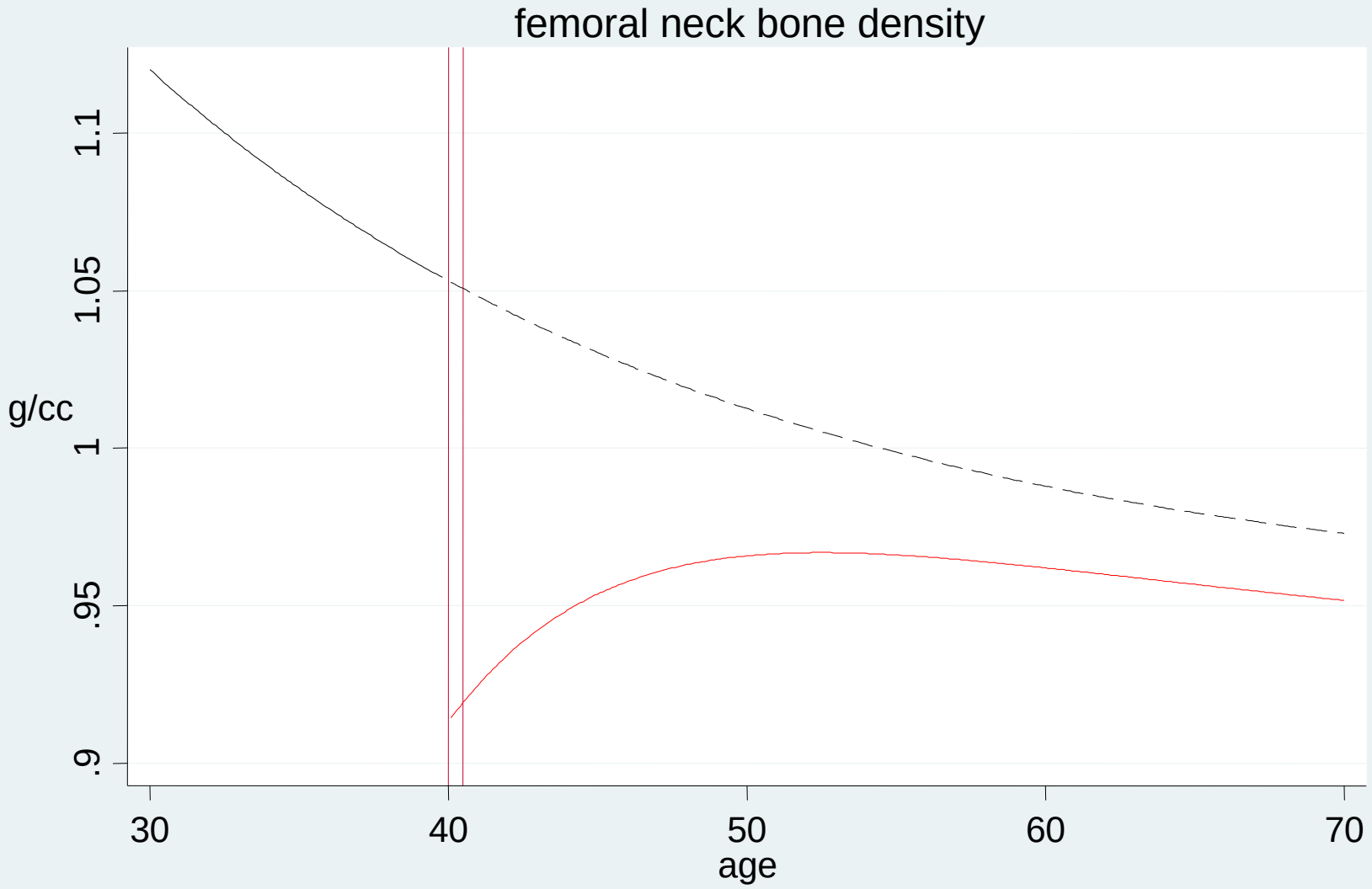
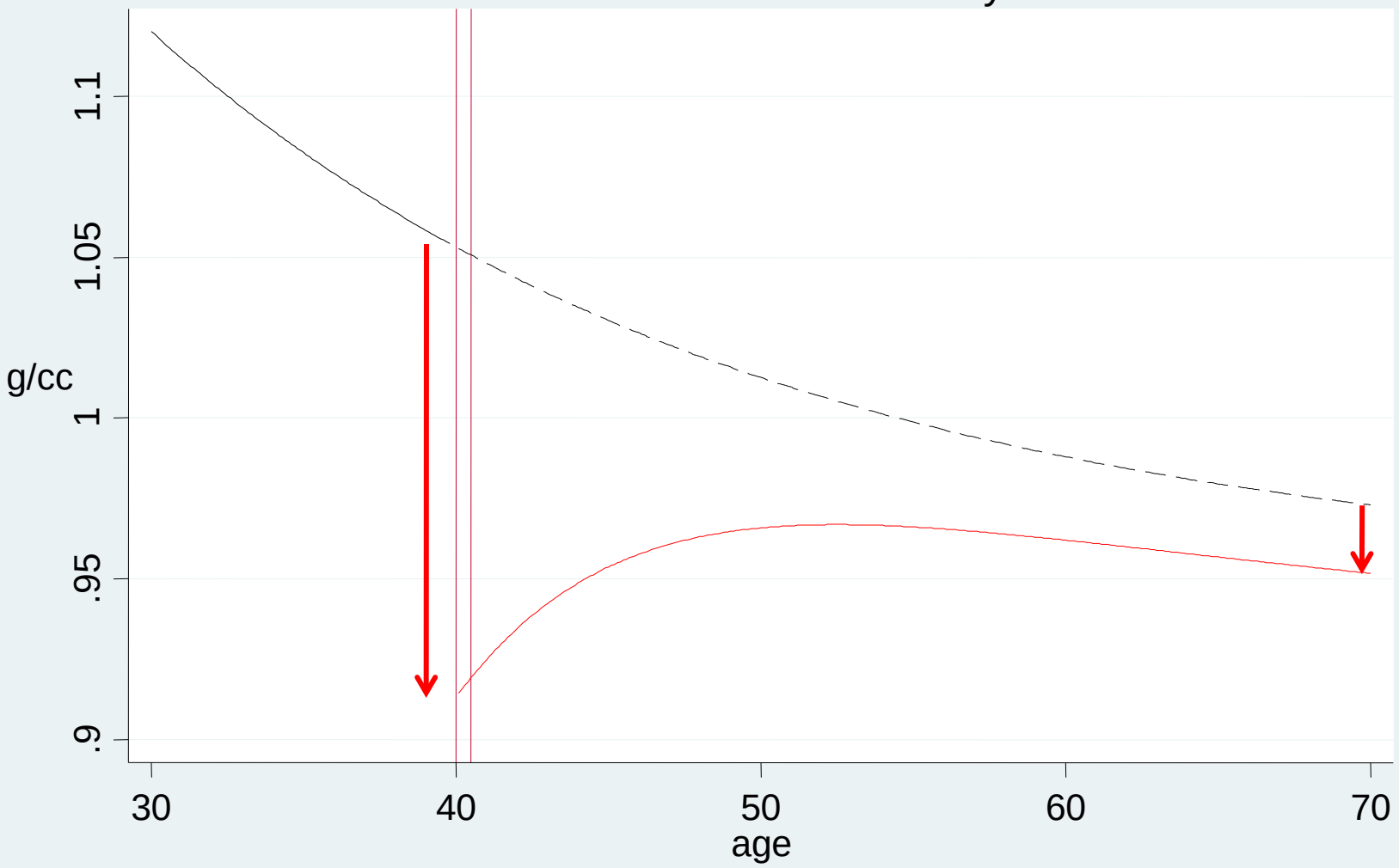
- exercise


longitudinal study of bone loss
femoral neck bone density
g/cc
.9
1
1.1
1.2
30
40
50
60
70
age

longitudinal study of bone loss



longitudinal study of bone loss



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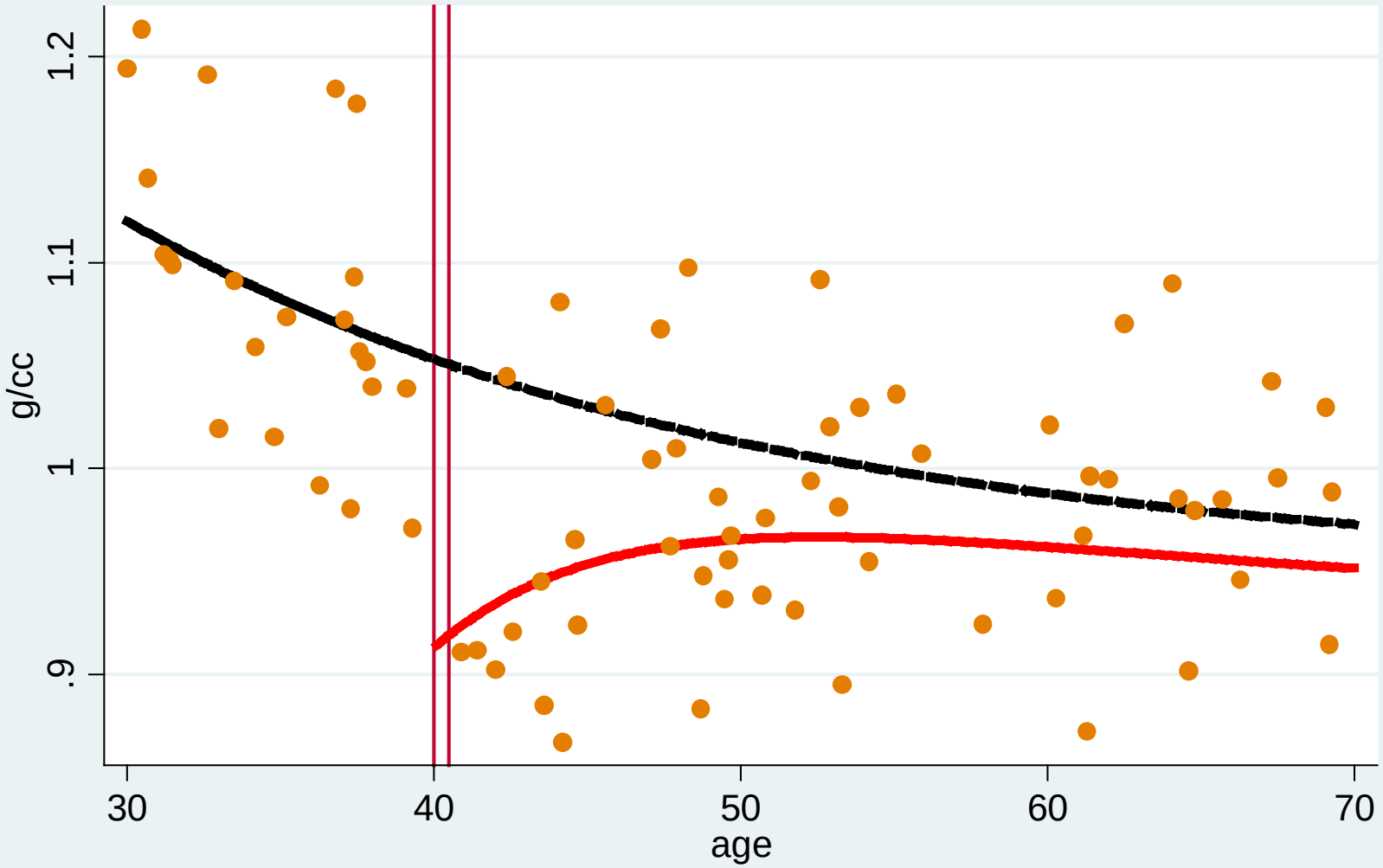

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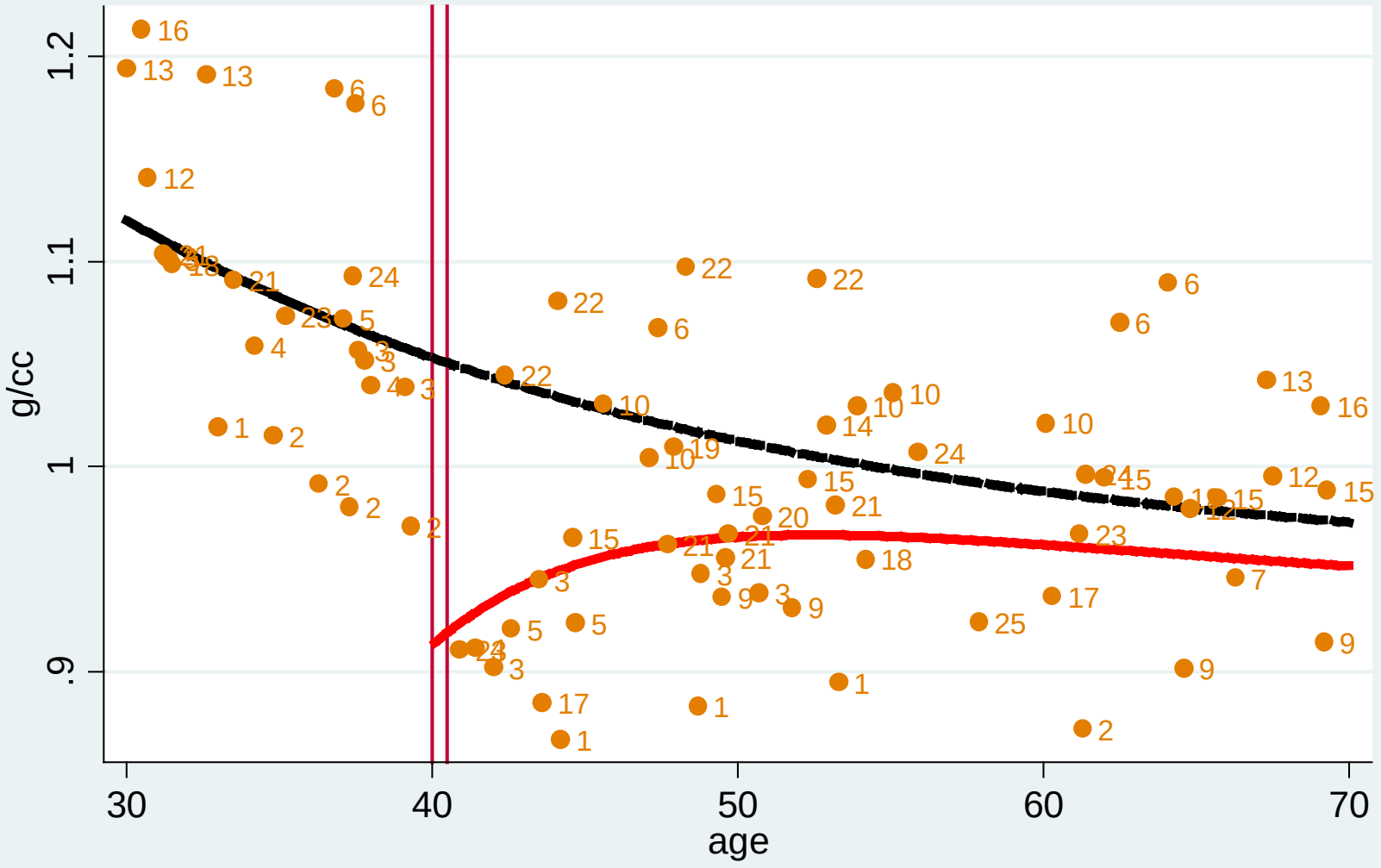

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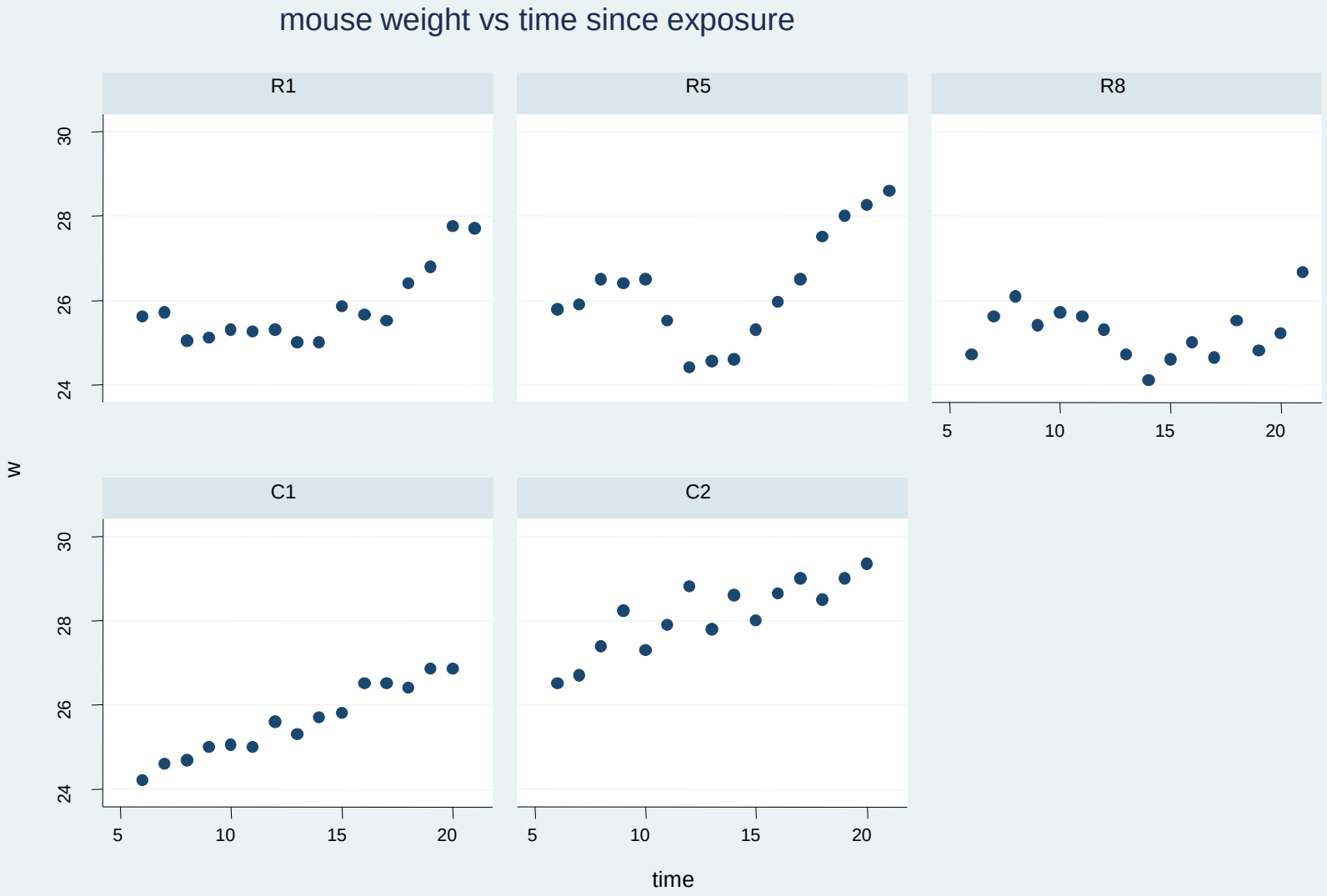
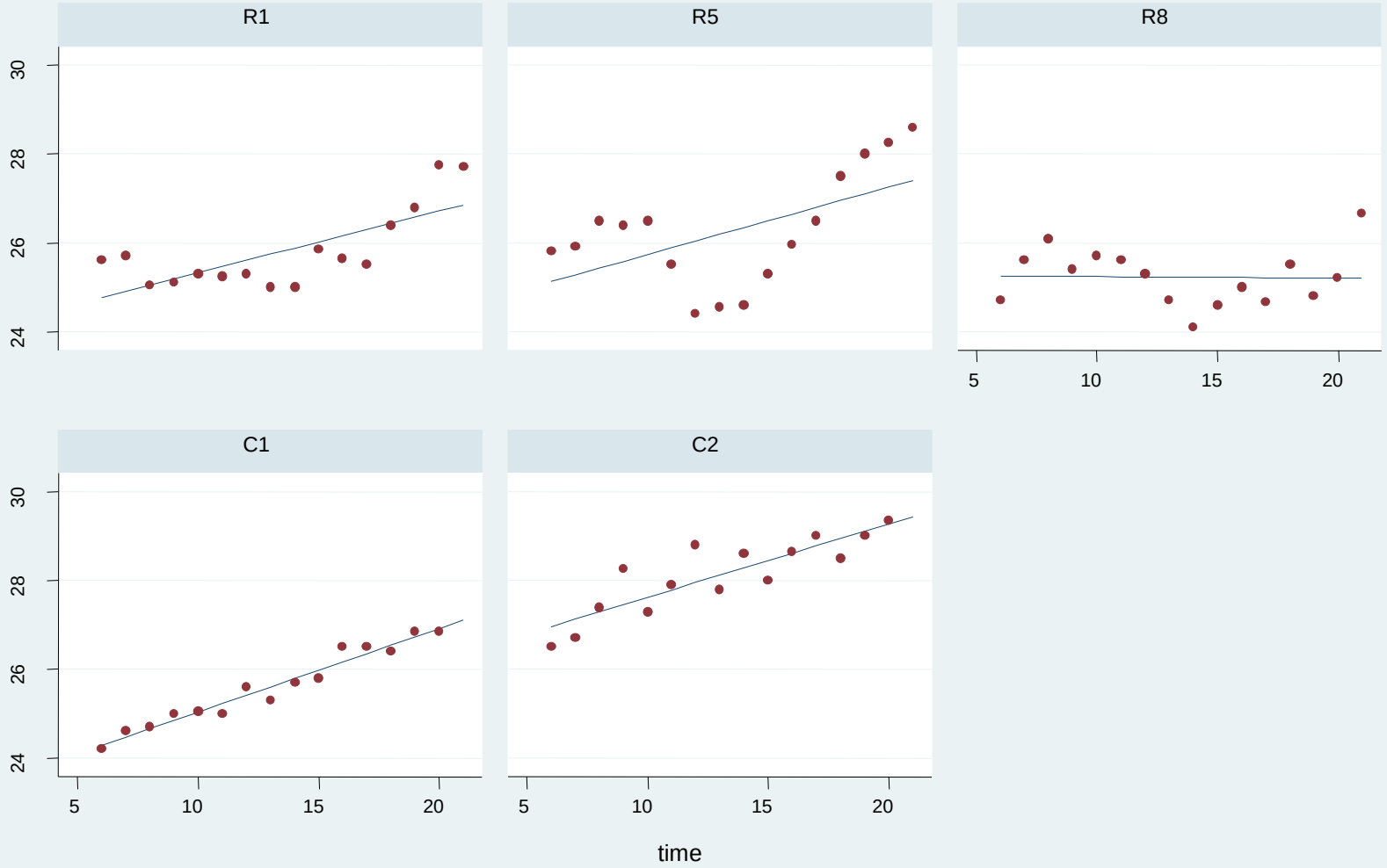


Graphs by Group I and sub within group

mouse weight vs time since exposure



Graphs by Group I and sub within group

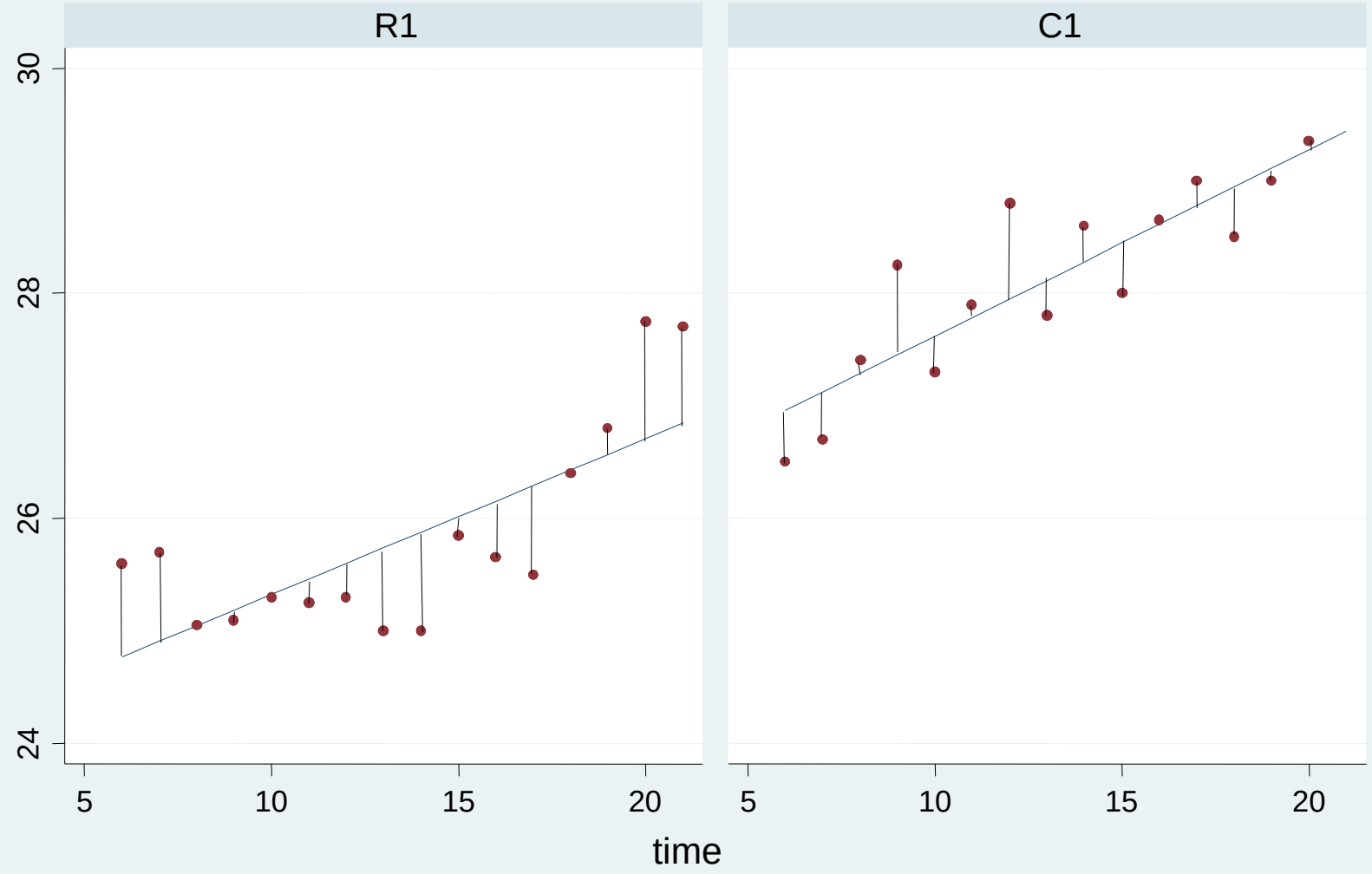
Distinguishing characteristic:

AR1 regression coefficient (L1)

- Control group:
- L1 small => random (high frequency variation)

- Radiation group:
- L1 large => carryover (low frequency variation)

mouse weight vs time since exposure



Graphs by sub within group

Examples of Projects, Data

- environmental physiology
- behavioral health and performance
- neurological
- bone
- radiation
- exercise

Exercise data - (27 ISS astronauts)

Predictors:

x1 TVIS sessions per week
x2 TVIS avg session time
x1x2 TVIS min/week
x5 ln[-(TVIS Load(lbs)) + 134.4]
x6 TVIS mph

x7 CEVIS avg session time
x8 CEVIS sessions per week
x7x8 CEVIS min/week

x13 RED avg squat load
x14 ln[(RED avg DL load) -110.9]

Exercise data (cont.)

Outcomes :

y1 Post-Pre Alk Phos
y2 Post-Pre NTELO
y3 Post-Pre Osteo
y4 Post-Pre BSAP

y5 Post-Pre Lspine BMD
y6 Post-Pre fneck BMD
y7 ln[-(Post-Pre troc BMD)+.0183]
y8 ln[-(Post-Pre whoebody BMD) + .0098]
y9 Post-Pre calc BMD
y10 Post-Pre pelvis BMD

Exercise data (cont.)

Outcomes (cont.)

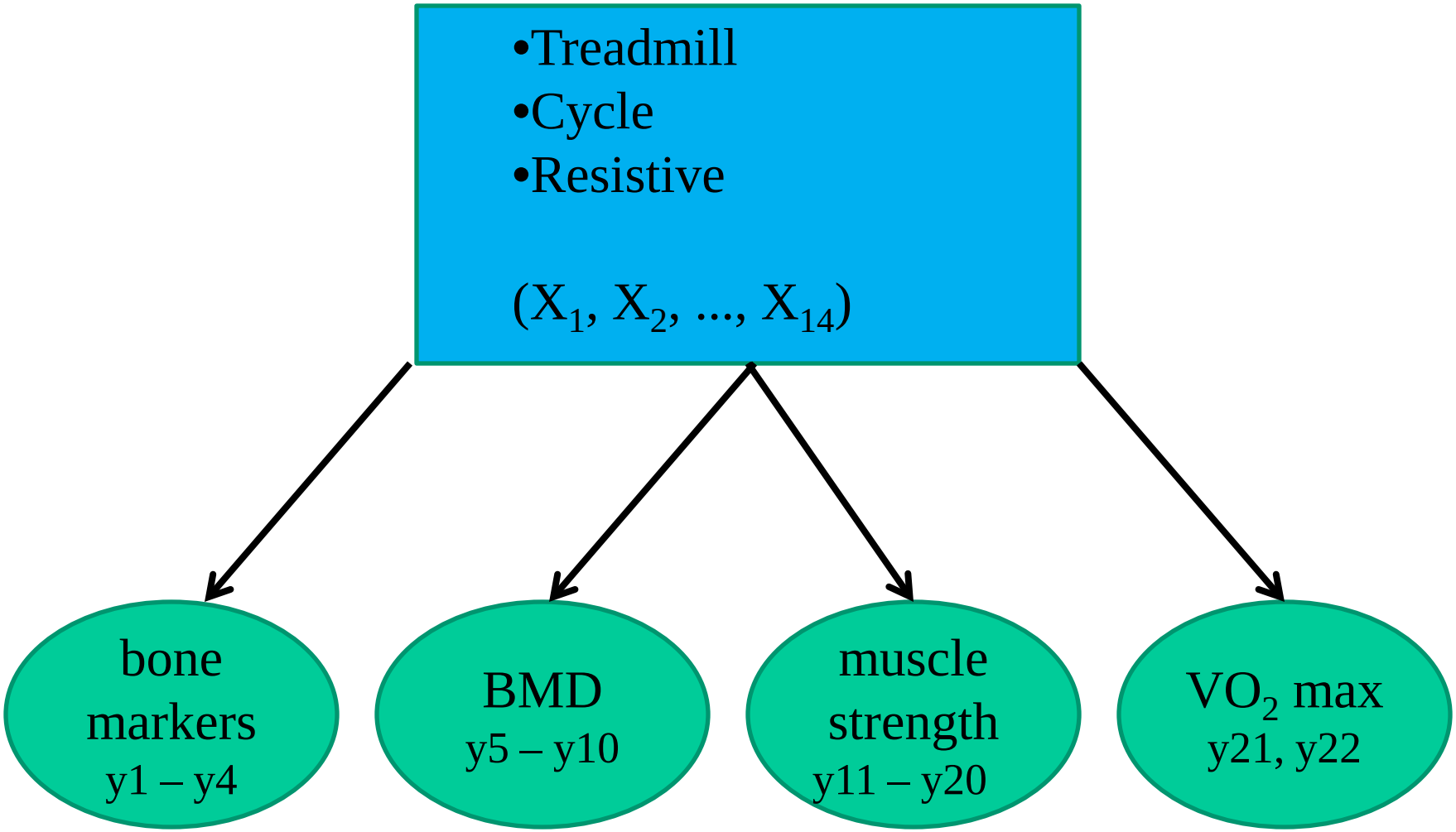
y11 Post-Pre Back Ext
y12 Post-Pre Trunk Flex
y13 Post-Pre Ankle Consentric Plantar
y14 Post-Pre Ankle Consentric Dorsi
y15 Post-Pre Ankle Eccentric Plantar
y16 Post-Pre Ankle Eccentric Dorsi
y17 Post-Pre Hamstring Total Work
y18 Post-Pre Hamstring Strength
y19 Post-Pre Quads Total Work
y20 Post-Pre Quads Strength

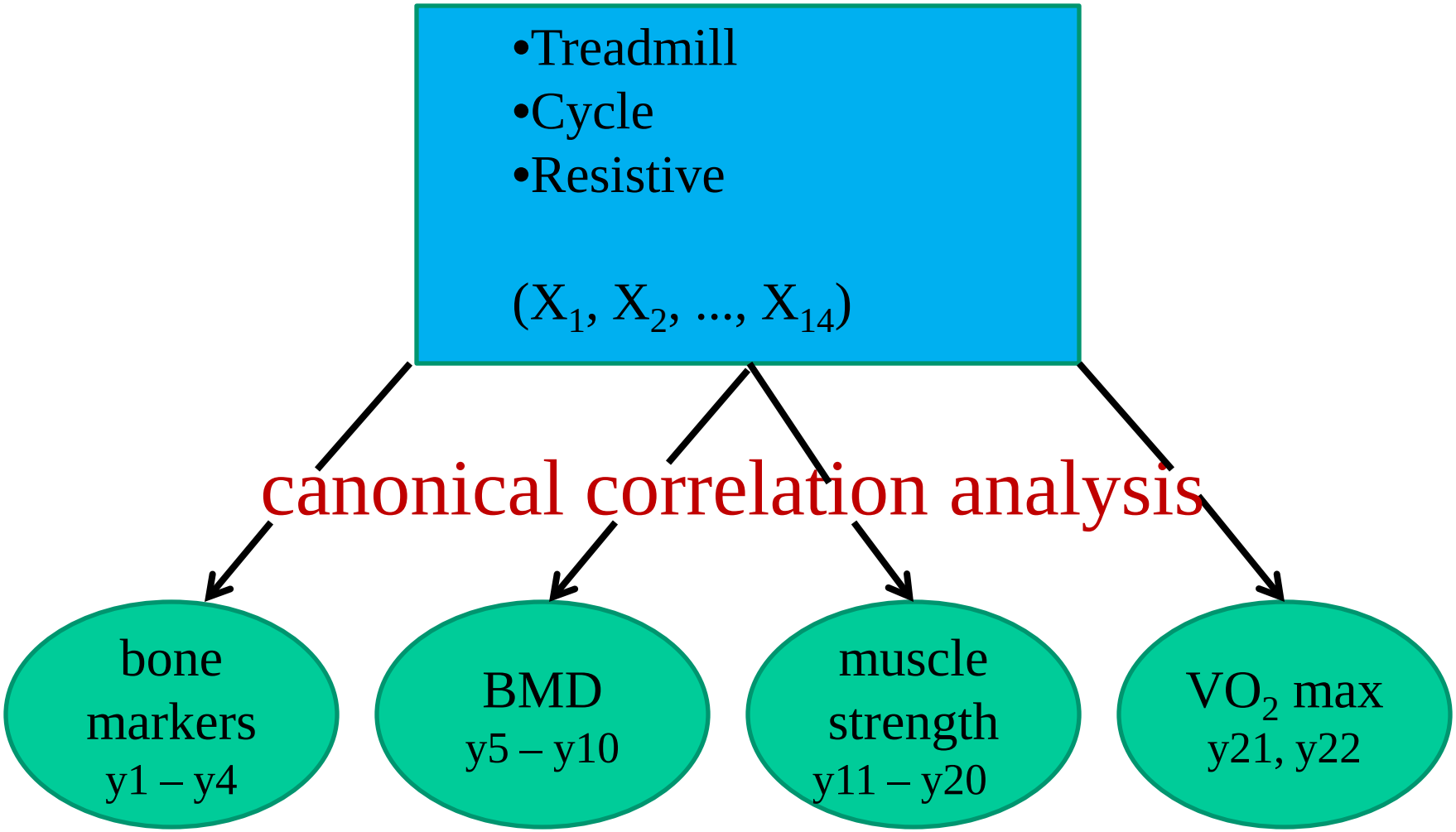
y21 Post-Pre Estimated VO2 (raw)
y22 Post-Pre Weight-Adjusted Estimated VO2

Main Research Questions

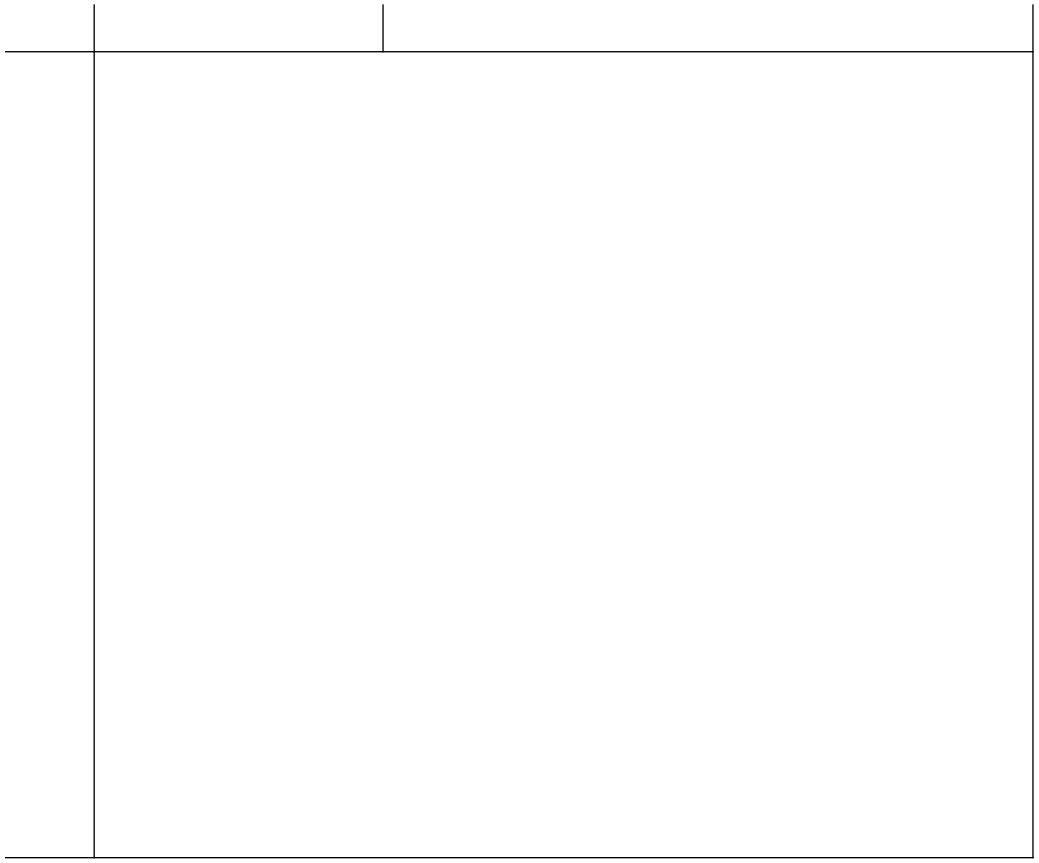
Does exercise (in general) mitigate the adverse effects of space on these outcomes (bone markers, bone mineral density, muscle strength, fitness level (VO2))?

If so, which aspects of exercise appear to have the most important effects?

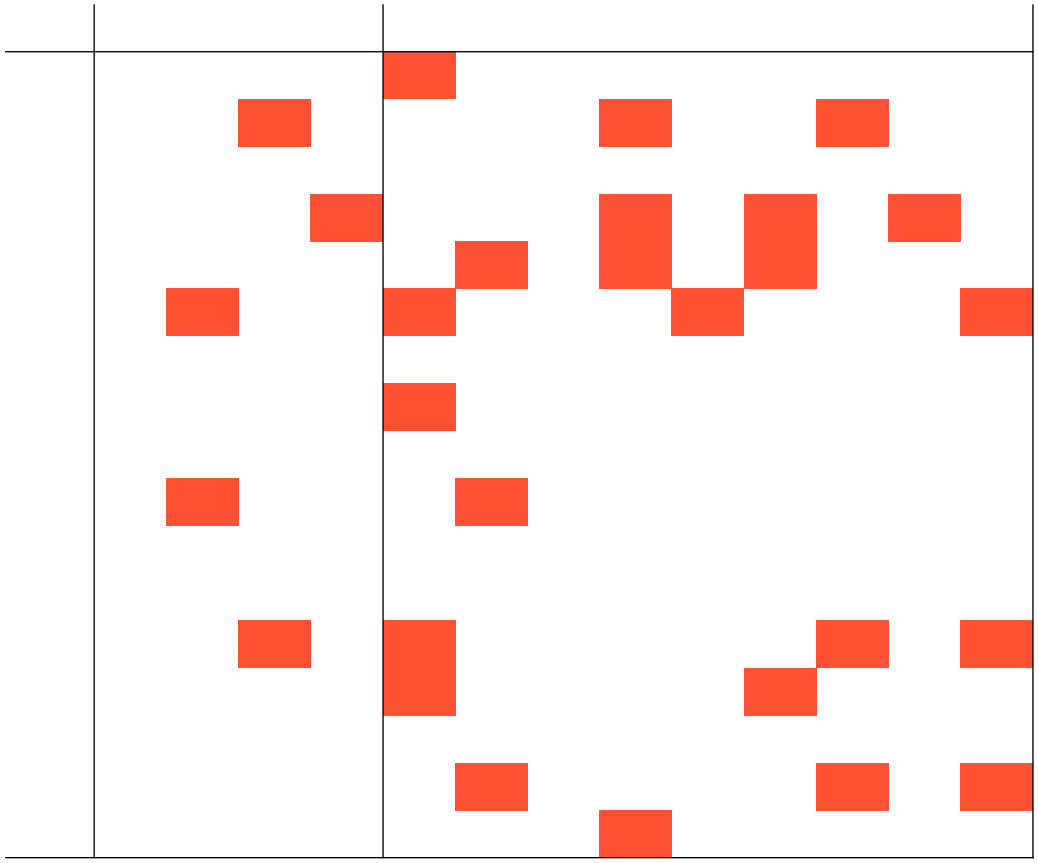

•Treadmill
•Cycle
•Resistive
$(X_1, X_2, ..., X_{14})$
bone markers
y1 – y4
BMD
y5 – y10
muscle strength
y11 – y20
VO_2 max
y21, y22


•Treadmill
•Cycle
•Resistive
$(X_1, X_2, ..., X_{14})$
canonical correlation analysis
bone markers
y1 – y4
BMD
y5 – y10
muscle strength
y11 – y20
VO_2 max
y21, y22

Data Matrix



Missing data



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